Asymmetric Synthesis of (-)-Neopodophyllotoxin

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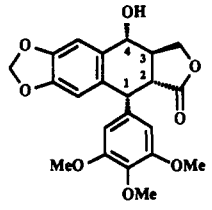
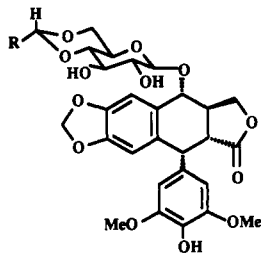
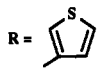
A five-step asymmetric synthesis of neopodophyllotoxin in 18% overall yield and optical purity >97%, starting from 6-(3,4,5-trimethoxybenzyl)piperonal (6) and the fumarate of (*S*)-methyl mandelate (8), is described.

Among the aryltetralin lignans isolated from nature, podophyllotoxin is one of the most well known because of its antimitotic activity[1,2] and the fact that two of its derivatives, etoposide[1,3] (VP-16-213) and teniposide[1,2] (VM-26), are in clinical use as anticancer agents. Because of



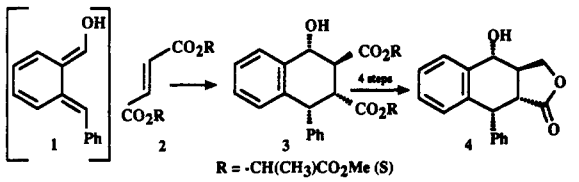
Podophyllotoxin



R =  , Teniposide R = Me, Etoposide

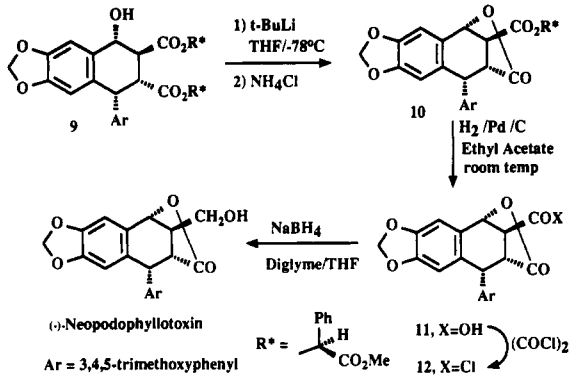
its biological activity and its rather challenging stereochemistry, a great deal of interest has been shown in the synthesis of podophyllotoxin. In the earliest work, racemic podophyllotoxin was synthesized by converting its C-2 epimer, picropodophyllotoxin, to podophyllotoxin by a kinetic quenching of its enolate.[4-6] While more recent syntheses of racemic podophyllotoxin have avoided this inefficient step,[7-11] it was still used in the first of the two asymmetric total syntheses of (-)-podophyllotoxin that have been published.[12,13] Total syntheses of(±)-epipodophyllotoxin[11,14] (epimeric at C-4), (±)-epiisopodophyllotoxin[15,16] (epimeric at C-4 and C-1), and (±)-4-deoxypodophyllotoxin[17] have been published as well as asymmetric syntheses of (-)-deoxypodophyllotoxin[18] and

Scheme I



R = -CH(CH$_3$)CO$_2$Me (S)

Scheme II



(-)-epiisopodophyllotoxin.[19] A recent paper on the synthesis of (±)-podophyllotoxin also included the syntheses of seven of the other *Podophyllum* lignans.[7]

In our own work on the asymmetric synthesis of lignans and ligan analogues, we have discovered that the fumarate of (*S*)-methyl lactate adds to α-hydroxy-*o*-quinodimethanes with very high diastereoselectivity,[20] and we have used this reaction for the preparation of an analogue of podophyllotoxin (4) (see Scheme I).[21]

The diastereomeric excess (de) for the cycloaddition of 1 with 2 was greater than 95%, providing the cycloadduct 3 having the *cis*-1,2-*trans*-2,3-*trans*-3,4 podophyllotoxin stereochemistry.

We have also recently found that the fumarate of methyl mandelate adds to α-hydroxy-*o*-quinodimethanes with the same high selectivity as shown by the fumarate of methyl lactate.[22] We would now like to report on the use of this latter reaction for a short asymmetric synthesis of (-)-neopodophyllotoxin (Scheme II).

Results and Discussion

o-Quinodimethane 5 can be generated photochemically from the aldehyde 6[15] or, in principle, thermally from benzocyclobutenol 7. While the synthesis of benzocyclobutenol 7 has been twice described in the literature, it has

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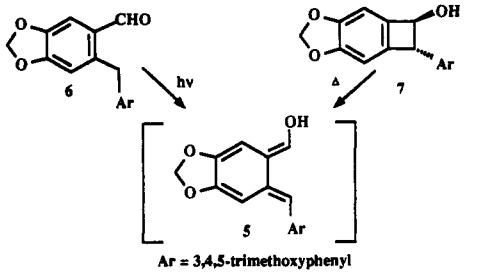
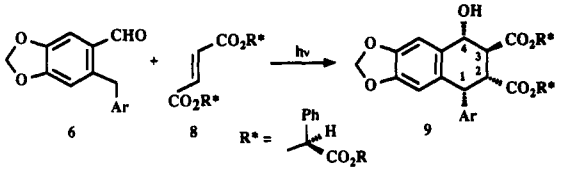
been found to be thermally unstable above 0 °C.[9,24] For this reason the more easily accessible aldehyde 6, prepared by the mthod of Sammes,[25] was chosen as the precursor to *o*-quinodimethane 5.



Ar = 3,4,5-trimethoxyphenyl

The fumarate of (*S*)-methyl mandelate (8) was prepared in 90% yield by heating fumaryl chloride with (*S*)-methyl mandelate[26] (2 equiv) at 110 °C for 15 h. A benzene solution of aldehyde 6 and 1 equiv of the fumarate was irradiated under nitrogen at room temperature using a medium pressure mercury lamp and a Pyrex filter. A further 2 equiv of fumarate (in benzene solution) was added dropwise to the irradiated solution over a period of 5 h. ^{1}H NMR (300 MHz) of the crude product showed that signals due to two isomeric adducts were present (ratio of major:minor = 8:2 by NMR integration). Chromatography of the crude reaction mixture gave the two adducts in a total yield of 45%. Unfortunately the major isomer could not be fully separated from the minor isomer and hence the minor isomer could not be fully characterized. A small sample of the pure major adduct was isolated by careful rechromatography of the isomeric mixture. It exhibited a doublet for H-1 at 4.50 ppm with a $J_{1,2}$ of 5.80 Hz and doublet of doublets for H-4 at 4.95 ppm with a $J_{3,4}$ of 9.32 Hz. These coupling constants suggested a 3,4-*trans* and 1,2-*cis* stereochemistry. A similar adduct with 3,4-*trans* and 1,2-*cis* stereochemistry, obtained from the exo addition of the fumarate of (*S*)-methyl lactate to α-hydroxy-α′-phenyl-*o*-quinodimethane, exhibited a $J_{1,2}$ of 5.70 Hz and a $J_{3,4}$ of 9.5 Hz.[21] An adduct with 1,2-*trans* stereochemistry exhibited a $J_{1,2}$ of 10 Hz.[15] On the basis of previous experience with the cycloaddition of the fumarate of (*R*)-methyl mandelate with α-hydroxy-*o*-quinodimethane (exo addition) and analogy to similar compounds, the above major adduct was assigned structure 9. Treatment of the



above isomeric mixture of two cycloadducts with *t*-BuLi at −78 °C followed by mild acid quenching furnished essentially a single product in 54% yield after chromatography.[27] NMR of the product indicated that elimination of one molecule of mandelate had occurred and IR showed the presence of a lactone carbonyl at 1787 cm^{-1}. The lactone was assigned structure 10. Lactone formation between a 4-hydroxyl and a 2-carboxyl group under similar reaction conditions has been previously described.[21] Hydrogenolysis of 10 over 5% Pd/C in ethyl acetate at room temperature occurred selectively to give the corresponding lactone–carboxylic acid 11 in 87% yield. The selective hydrogenolysis of a group at the 3-position of a similar molecule has been reported by Kaneko and Wong.[10] The lactone–acid was treated with oxalyl chloride ($(COCl)_2$) to form the corresponding acid chloride 12, which was not characterized but was directly reduced with sodium borohydride in diglyme/THF to furnish the target compound neopodophyllotoxin in 88% yield (from 11). The proton NMR of the synthetic neopodophyllotoxin was identical to that previously reported[7,23] and when its optical activity is compared with that reported by von Wartburg et al.,[23] the optical purity is calculated to be 97%.

Conclusion

An asymmetric synthesis of (-)-neopodophyllotoxin has been accomplished in five steps in an overall yield of 18%, starting from aldehyde 6 and fumarate 8. Since neopodophyllotoxin has been converted to podophyllotoxin in 54% yield without configurational alteration,[10,23] the above synthetic route also constitutes an asymmetric synthesis of podophyllotoxin.

Experimental Section

General. ^{1}H NMR spectra were recorded at 300 MHz. Merck kieselgel 60 was used for all chromatography. Melting points were measured on a hot stage instrument and are uncorrected. *J* values are in hertz.

Fumarate of (*S*)-Methyl Mandelate (8). Neat fumaryl chloride (1.35 g, 8.82 mmol) and (*S*)-methyl mandelate (2.94 g, 17.7 mmol) were stirred together at 110 °C for 15 h. The crude oil was chromatographed (15% EtOAc/hexanes) to give a colorless oil, which solidified on standing (3.60 g, 98%): mp 85–87 °C; $[\alpha]^{20}_D$ +115.5° (*c* 1.10, $CHCl_3$); IR (CH_2Cl_2) 1759 (CO), 1734 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 6 H, CO_2Me), 6.04 (s, 2 H), 7.06 (s, 2 H), 7.39–7.48 (m, 10 H, Ar). Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.07; H, 4.90. Found: C, 64.11; H, 4.91.

Cycloadduct 9. Aldehyde 6 (0.438 g, 1.33 mmol) in dry benzene (100 mL) was purged with N_2 continuously. One-third of a solution of the fumarate 8 (3 equiv, 1.64 g in 90 mL of benzene, purged with N_2) was added and the mixture was irradiated at rt (450-W Hanovia medium pressure mercury lamp, 1-mm Pyrex filter). The remaining fumarate solution was added dropwise over a period of 5 h. Total irradiation time was 6 h 30 min. The solvent was evaporated and the crude product was chromatographed (30% EtOAc/Hexanes) to give recovered aldehyde 6 (46 mg) and a colorless foam (399 mg, 45% based on reacted aldehyde), which NMR analysis indicated was a mixture of isomers. Careful rechromatography (20% EtOAc/hexanes) of the isomeric mixtures gave a small sample of the pure major isomer: mp 97–99 °C; $[\alpha]^{20}_D$ −23.7° (*c* 0.228, $CHCl_3$); IR (CH_2Cl_2) 3488 (OH), 1746 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.40 (dd, 1 H, *J* = 9.39, 12.61), 3.56 (s, 3 H), 3.60 (dd, 1 H, *J* = 12.56, 6.10), 3.61 (s, 6 H), 3.65 (s, 3 H), 3.72 (d, 1 H, *J* = 3.14, OH), 3.78 (s, 3 H), 4.50 (d, 1 H, *J* = 5.80, H_1), 4.94 (dd, 1 H, *J* = 2.70, 9.32, H_4), 5.49 (s, 1 H), 5.91 (s, 2 H), 6.17 (s, 2 H), 6.22 (s, 1 H), 6.37 (s, 1 H), 6.93–7.02 (m, 4 H), 7.10–7.50 (m, 7 H); MS *m/z* (relative intensity) 742 (M^+, 3), 576 (26), 410 (30), 408 (32), 365 (43), 107 (100), 79 (97); HRMS, calcd for $C_{40}H_{38}O_{14}$ 742.2262, found 742.2214. Anal. Calcd for $C_{40}H_{38}O_{14}$: C, 64.69; H, 5.16. Found: C, 65.04; H, 5.29.

Lactone 10. Cycloadduct 9 (isomeric mixture, 64 mg, 0.086 mmol) in dry THF (5 mL) was cooled to −78 °C under N_2. *t*-BuLi (1 equiv, 0.068 mL, 1.26 M in pentane) was added dropwise and the solution stirred for 5 min. The reaction flask was removed from the cold bath and stirred at rt for 15 min. An aqueous $NH_4^+Cl^-$ solution (10%, 15 mL) was added and stirring continued for a further 5 min. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined

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(26) (*S*)-(+)-Methyl mandelate was prepared by acid-catalyzed esterification of (*S*)-mandelic acid (Aldrich) in methanol: mp 53–55 °C; $[\alpha]^{20}_D$ +140.4° (*c* 0.39 CH_3OH); lit. (for (*R*)-(−)-methyl mandelate, mp 55 °; $[\alpha]^{18}_D$ −143° (CH_3OH); *Dictionary of Organic Compounds*, 4th ed.; Eyre & Spottiswoode Publishers Ltd., E. & F.N. Spon Ltd.: London, 1965; Vol. 4, p 2052.
(27) While the isolated product from this reaction derives from the major cycloadduct, the exact fate of the minor cycloadduct in this reaction is unknown.

organic phases were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Chromatography of the crude oil (40% EtOAc/hexanes) gave a microcrystalline solid (27 mg, 54%): mp 89–91 °C; $[\alpha]^{20}_D$ +5.27° (c 1.10, $CHCl_3$); IR (CH_2Cl_2) 1787 (lactone CO), 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.32 (dt, 1 H, J = 0.87, 4.82, H_2), 3.60 (s, 3 H), 3.75 (s, 6 H), 3.61 (s, 6 H), 3.84 (s, 3 H), 3.95 (t, 1 H, J = 5.08, H_3), 4.62 (d, 1 H, J = 4.69, H_1), 5.43 (d, 1 H, J = 4.90, H_4), 5.86 (s, 1 H), 5.97 (s, 2 H), 6.21 (s, 2 H), 6.43 (s, 1 H), 6.83 (s, 1 H), 7.32–7.42 (m, 5 H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 44.45 (CH), 46.51 (CH), 49.72 (CH), 52.67 (CH_3), 56.20 (CH_3), 60.83 (CH_3), 75.04 (CH), 77.55 (CH), 101.38 (CH_2), 106.70 (CH), 108.22 (CH), 110.30 (CH), 127.56 (CH), 128.06 (C), 128.90 (CH), 129.61 (CH), 129.77 (C), 133.05 (C), 136.41 (C), 137.47 (C), 146.55 (C), 148.55 (C), 153.03, (C), 166.53 (C), 167.90 (C), 173.36 (C); MS m/z (relative intensity) 577 (M^+ + 1, 12), 576 (M^+, 33), 410 (23), 339 (36), 107 (100), 79 (55); HRMS, calcd for $C_{31}H_{28}O_{11}$ 576.1632, found 576.1633.

Lactone–Acid 11. Lactone 10 (27 mg, 0.047 mmol) and 5% Pd/C (15 mg) in EtOAc (10 mL) were stirred under H_2 (1 atm) at rt for 2 h. The mixture was filtered, the filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 (20 mL). The solution was extracted with 5% aqueous $NaHCO_3$ (3 × 10 mL). The combined bicarbonate layers were acidified (10% HCl), saturated with NaCl, and extracted with EtOAc (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a colorless solid (17.5 mg, 87%). Crystals from CH_2Cl_2/hexanes had the following: mp 209–211 °C; $[\alpha]^{20}_D$ –26.7° (c 0.43, $CHCl_3$); IR (CH_2Cl_2) 3400–2800 (br, CO_2H), 1787 (lactone CO), 1734 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (t, 1 H, J = 4.75, H_2), 3.78 (s, 6 H, OCH_3), 3.85 (s, 3 H), 3.89 (t, 1 H, J = 5.05, H_3), 4.76 (d, 1 H, J = 4.77, H_1), 5.38 (d, 1 H, J = 5.12, H_4), 5.95, 5.97 (AB q, 2 H, J = 1.27, OCH_2O), 6.27 (s, 2 H, Ar H), 6.46 (s, 1 H, Ar H), 6.79 (s, 1 H, Ar H); MS m/z (relative intensity) 428 (M^+, 5), 382 (15), 338 (47), 323 (30), 81 (51), 73 (29), 69 (100); HRMS, calcd for $C_{22}H_{20}O_9$ 428.1107, found 428.1090.

(–)-Neopodophyllotoxin. Lactone–acid 11 (23.5 mg, 0.0549 mmol) in dry CH_2Cl_2 (3 mL, dried with 3-Å molecular sieves) and oxalyl chloride (5 mL) were stirred at rt for 4 days. The excess oxalyl chloride was evaporated; $NaBH_4$ (20 mg), dry THF (3 mL), and diglyme (1 mL) were added. The mixture was stirred for 2 h. Water (20 mL) was added and stirring continued for half an hour (until all the excess $NaBH_4$ was destroyed). The solution was saturated with NaCl and the organic phase separated. The aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined extracts were dried ($MgSO_4$) and evaporated. Recrystallization of the crude product (EtOAc/hexanes) gave a colorless solid (20 mg, 88%): mp 232–234 °C (lit.[7] mp 230–231 °C); $[\alpha]^{20}_D$ –50.8° (c 0.26, $CHCl_3$), lit.[23] $[\alpha]^{20}_D$ –52.4°; IR (CH_2Cl_2) 3617 (OH), 3330 (OH), 1781 (lactone CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (t, 1 H, J = 4.38, H_2), 3.16 (m, 1 H, H_3), 3.66 (dd, 1 H, J = 7.69, 10.82), 3.75 (1 H, overlapped by OMe singlet), 3.78 (s, 6 H, OMe), 3.85 (s, 3 H, OMe), 4.25 (d, 1 H, J = 4.54, H_1), 5.19 (d, 1 H, J = 4.75, H_4), 5.95, 5.97 (AB q, 2 H, J = 1.30, OCH_2O), 6.28 (s, 2 H, Ar H), 6.49 (s, 1 H, Ar H), 6.74 (s, 1 H, Ar H); MS m/z (relative intensity) 415 (M^+ + 1, 11), 414 (M^+, 54), 394 (36) 339 (19), 98 (32), 69 (100); HRMS, calcd for $C_{22}H_{22}O_8$ 414.1315, found 414.1304. The ^1H NMR data are identical to those previously published.[7,23]

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Supplementary Material Available: ^1H NMR spectra for compounds 8–11 and (–)-neopodophyllotoxin (5 pages). Ordering information is given on any current masthead page.

Syntheses and Ion Selectivity of Conformational Isomers Derived from Calix[4]arene

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Three conformational isomers (cone, partial cone, and 1,3-alternate) of 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)methoxy]-26,28-bis(2-pyridylmethoxy)calix[4]arene (3) were synthesized from 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(2-pyridylmethoxy)calix[4]arene (6). The examination of the metal selectivity in two-phase solvent extraction established that the cone conformer predominantly results when the base contains template metal cations, whereas the partial cone and 1,3-alternate conformers result when the base contains nontemplate metal cations. The solvent extraction data indicated that cone-3 shows the strong metal affinity as comparable with that of cone-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (cone-2) and binds not only Na^+ but Li^+. On the other hand, partial-cone-2 shows a poor metal affinity. The difference was discussed on the basis of spectroscopic and X-ray crystallographic data. This paper demonstrates for the first time that the metal selectivity of ionophoric calix[*n*]arenes can be changed not only by the change in the ring size but also by the conformational change.

Introduction

Calixarenes have been used as useful basic skeletons for the synthesis of lipophilic,[1-3] water-soluble,[4] and ionophoric receptors.[5-8] For the design of these functionalized calixarenes, modification of OH groups arranged on the lower rim is convenient.[9,10] Among them, the ionophoric properties of calix[4]arene derivatives are of particular interest: for example, 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene with a cone conformation (cone-2), prepared by the reaction of

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‡ University of Maryland.

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