A Highly Stereoselective Synthesis of Podophyllotoxin and Analogues Based on an Intramolecular Diels-Alder Reaction†

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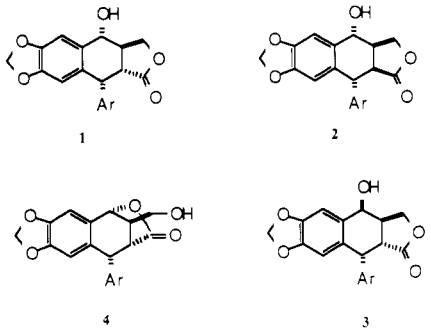
A synthesis of podophyllotoxin and several analogues is described. The key step that generates all four chiral centers of podophyllotoxin involves an intramolecular Diels-Alder reaction between an appropriately substituted *o*-quinodimethane and a pendant crotonate moiety. Thus *trans*-2-(3,4,5-trimethoxyphenyl)-4,5-(methylenedioxy)benzocyclobutenol (**7**) was coupled with the isocyanate derived from methyl *trans*-4-aminocrotonate to yield urethane **16**. Thermolysis of urethane acid **18**, derived from **16** by ester hydrolysis, in nitromethane at 100 °C gave in greater than 60% yield a 5:1 mixture of tricyclic urethane **20** and its cis-fused isomer. Basic hydrolysis of **20** generated a γ-amino acid, which was diazotized to yield podophyllotoxin. Two analogues of podophyllotoxin were prepared via a similar route. An interesting variation in the endo/exo ratio with changes in the solvent polarity of the intramolecular Diels-Alder reaction involving the *o*-quinodimethane and the pendant crotonate moiety was observed.

Introduction

Podophyllotoxin (**1**) is of considerable interest as a synthetic target since it serves as precursor to the clinically used anticancer drug Etoposide.[1] Several syntheses of



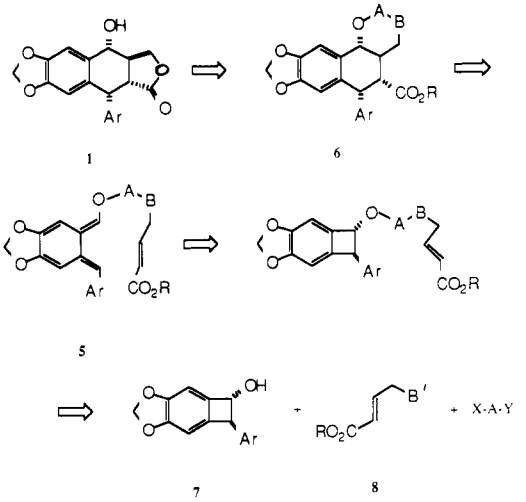
Ar= 3,4,5-trimethoxyphenyl, here and throughout this paper.

podophyllotoxin have been reported in the past decade. Typically the syntheses have led to an isomer of podophyllotoxin such as picropodophyllin (**2**),[2] epipodophyllotoxin (**3**),[3] or neopodophyllotoxin (**4**).[4] These isomers have previously been converted to podophyllotoxin. Either podophyllotoxin or the epi isomer **3** can serve as precursor to Etoposide.[3,4]

We have recently described in a communication a synthesis of podophyllotoxin based on an intramolecular Diels-Alder reaction as shown in retrosynthetic form in Scheme I.[5] The key feature of this approach is the thermal conrotatory opening of an appropriately substituted benzocyclobutenol to generate the *o*-quinodimethane **5**, which was expected to undergo an intramolecular Diels-Alder reaction to furnish preferentially the tricyclic intermediate **6** in which all four of the chiral centers of podophyllotoxin had been established with the correct relative stereochemistry. The method required for elaboration of the γ-lactone would depend on the nature of the linkage between the benzocyclobutenol **7** and the crotonate moiety **8**.

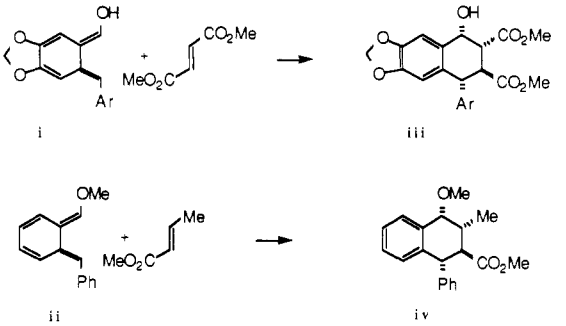
An intramolecular rather than intermolecular Diels-Alder approach was necessary in order to establish the relative stereochemistry of the substituents that would eventually form the CD ring of podophyllotoxin. Thus, for example, intermolecular trapping of dienol i with dimethyl fumarate[6a] or methoxy derivative ii with methyl

Scheme I[a]



[a] A = CO; B = O or NH. X and Y are leaving groups.

crotonate[6b] gave almost exclusively products iii and iv in which the aryl and the adjacent carboethoxy groups had the trans rather than the required cis relationship.



† Dedicated to Prof. E. J. Corey on the occasion of his 60th birthday.

(1) Jardine, I. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Doures, J. D., Eds.; Academic: New York, 1980; pp 319-351.

(2) Picropodophyllin: (a) Gensler, W. J.; Gatsonis, C. *J. Org. Chem.* **1966**, *31*, 4004. (b) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082; **1981**, *103*, 6208.

(3) Epipodophyllotoxin: (a) Van der Eycken, J.; DeClerqu, P. Vanderwalle, M. *Tetrahedron Lett.* **1985**, *26*, 3871. Vyas, D. M.; Skonezny, P. M.; Jenks, T.A.; Doyle, T. W. *Tetrahedron Lett.* **1986**, *27*, 3099.

(4) Neopodophyllotoxin: (a) Rajapska, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208. (b) Kaneko, T.; Wong, H. *Tetrahedron Lett.* **1987**, *28*, 517.

(5) Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1986**, *51*, 4749.

(6) (a) Glinski, M. B.; Durst, T. *Can. J. Chem.* **1983**, *61*, 573. (b) Khan, Z.; Durst, T. *Can. J. Chem.* **1987**, *65*, 482.

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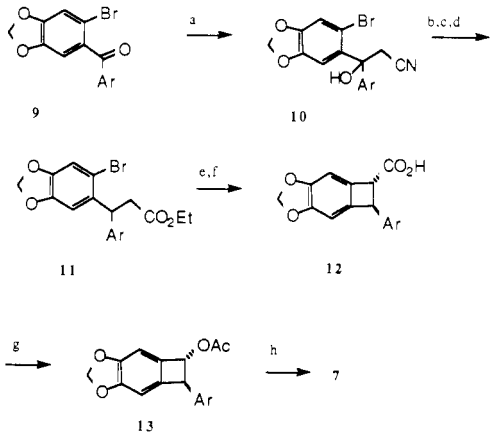
Scheme II[a]



[a] Reagents: (a) $LiCH_2CN$; (b) H^+; (c) Mg/MeOH/THF/−36 °C; (d) HCl/EtOH, then H_2O; (e) $4NaNH_2/NH_3$/−78 °C; (f) KOH/DMSO/H_2O; (g) $Pb(OAc)_4$/HOAc/20 °C; (h) HCl/MeOH/−10 °C/5 h.

Discussion and Results

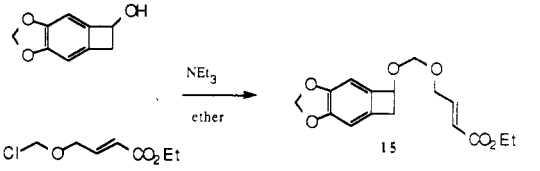
At the beginning of this work no examples of *trans*-2-arylbenzocyclobutenols had been described in the literature. Jung and co-workers[7a] had discussed in considerable detail their attempts to prepare such compounds by applying methods that had served well for the synthesis of benzocyclobutenols that did not carry a 2-aryl substituent; however, none of their approaches were successful for **7** or analogues thereof. We had also initially attempted to prepare **7** by the same types of routes and were also unsuccessful.[7b] Our eventually successful approach to **7** and an analogue of **7** is shown in Scheme II.[8]

Benzophenone **9**, available in three steps from piperonal,[9] was reacted with lithioacetonitrile in THF at −78 °C to give alcohol **10**, mp 171–172 °C, in 97% yield. Acid-catalyzed dehydration gave a mixture of alkenes which was reduced with magnesium in methanol–THF at −36 °C to afford a saturated nitrile, which upon treatment with ethanolic HCl followed by water gave ester **11** in 84% overall yield. Reaction of this ester with 4 equiv of sodium amide in liquid ammonia[10] at −78 °C for 10 min furnished, via a benzyne intermediate, in 42% yield a 1:1 mixture of *cis*- and *trans*-benzocyclobutene esters which upon treatment with KOH in aqueous DMSO underwent isomerization and saponification to give benzocyclobutene carboxylic acid **12** (85%). Oxidative decarboxylation of acid **12** with lead tetraacetate in THF–acetic acid at 17–20 °C afforded the key *tran*-2-(3,4,5-trimethoxyphenyl)-benzocyclobutyl acetate **13** in 74% yield. This compound, mp 134–135 °C, was characterized by an infrared band at 1735 cm^{-1} and a 3 H singlet at 2.12 ppm due to the acetate group as well as two doublets at 4.38 and 5.45 ppm (J = 1.8 Hz, 1 H each) due to the dibenzylic and the hydrogen α to the acetoxy group in its proton NMR spectrum. The 1.8-Hz coupling constant between the two hydrogens indicates a trans relationship about the cyclobutane ring. Careful control of the temperature was required and the use of only 1 equiv of lead tetraacetate was critical. Large amounts of a byproduct containing an acetate on the methylenedioxy bridge were obtained when the temperature was too high or excess oxidant was employed.

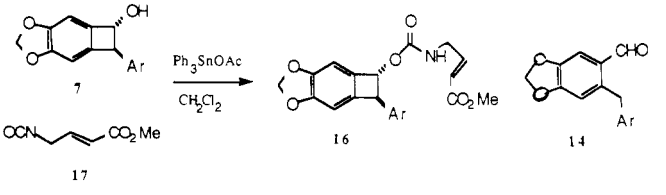
Cleavage of the acetate function in **13** to give the desired alcohol **7** occurred at −10 °C in methanol–methylene chloride–HCl in 5 h. The alcohol showed the expected infrared peak at 3200–3500 cm^{-1} due to the hydroxyl group; its proton NMR displayed singlets at δ 3.80 (6 H), 3.82 (3 H), 4.17 (1 H), 4.77 (1 H), 6.20 (2 H), 6.71 (1 H), and 6.84 (1 H) and two doublets at δ 5.93 (J = 2.0 Hz) and 5.96 (J = 2.0 Hz). The fact that the coupling constant for the two cyclobutane hydrogens at δ 4.17 and 4.77 is negligibly small confirms the retention of the trans stereochemistry. The signal for the OH peak was found to be variable and in the 4.5–4.8 ppm range.

Alcohol **7** was found to be extremely labile. If the methanolysis was carried out at temperatures above 0 °C or if basic conditions were employed, partial or complete conversion to aldehyde **14**[11] was observed. Even short periods of standing in neutral solution at 25 °C or concentrating of solutions of **7** resulted in considerable formation of **14**. Due to this extreme instability alcohol **7** was stored as acetate **13**. This instability of **7** relative to benzocyclobutanol itself was unexpected and probably explains the earlier difficulties encountered in preparing this compound. A second synthesis of **7** that is quite similar to ours and also utilizes the intramolecular trapping of a benzyne to generate the benzocyclobutene ring has also been published.[12]

We had initially intended to couple benzocyclobutenol **7** to 4-hydroxycrotonate in the form of a mixed carbonate. This approach had to be abandoned since the formation of mixed carbonates from two alcohols and phosgene or carbonyldiimidazole requires a basic catalyst such as triethylamine. Such reaction conditions are not tolerated by **7**. We also considered tethering the dienophile to **7** via a mixed acetal. Such a scheme had been successful in the preparation of the model compound **15**, but in this case, too, basic reaction conditions were employed.[9] An attempt to join **7** to the chloromethyl ether of 4-hydroxycrotonate using silver salt catalysis was unsuccessful.[7b]



Eventually the fragments were joined in the form of a carbamate i.e., **16**. The formation of **16** proceeded in 47% yield when isocyanate **17**, prepared in 57% yield from



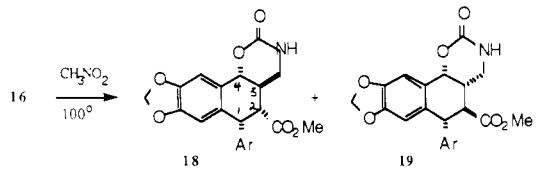
methyl *trans*-4-aminocrotonate hydrochloride[13] and phosgene in refluxing toluene, was mixed with benzocyclobutanol **7** in methylene chloride at 0 °C in the presence of triphenyltin acetate as catalyst[14] and the so-

(7) (a) Jung, M. E.; Lam, P. Y.-S.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087. (b) Macdonald, D. I. Ph.D. Thesis, University of Ottawa, 1987.
(8) Macdonald, D. I.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 2235.
(9) Glinski, M. B. Ph.D. Thesis, University of Ottawa, 1982.
(10) (a) Bunnett, J. F.; Skorcz, J. A. *J. Org. Chem.* **1962**, *27*, 3836. (b) Skorcz, J. A.; Kaminski, F. E. *J. Med. Chem.* **1965**, *8*, 732.
(11) (a) Sammes, P. G. *Tetrahedron*, **1976**, *32*, 405. (b) Arnold, B. J.; Mellows, S. M.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1266.
(12) Jung, M. E.; Lowen, G. T. *Tetrahedron Lett.* **1986**, *27*, 5319.
(13) (a) Pinza, M.; Pifferi, G. *J. Pharm. Sci.* **1978**, *67*, 120. (b) Brehm, L.; Jacobsen, P.; Johansen, J. S.; Krogsgaard-Larson, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1459.
(14) Ozaki, J. *Chem. Rev.* **1984**, *84*, 205.

lution was concentrated to a thick oil.

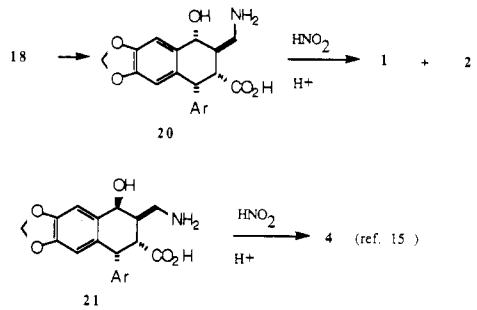
Urethane **16**, mp 141–142 °C, showed in addition to the expected aromatic and methylenedioxy signals two doublets at 4.36 and 5.47 ppm (J = 0.6 Hz, 1 H each) due to the two benzocyclobutene ring protons, a singlet at 3.72 ppm (OCH_3), a multiplet at 4.00 ppm (2 H, $NHCH_2$), a broad signal at 4.90 ppm due to NH, and two doublets of triplets at 5.96 and 6.92 ppm, with coupling constants of 15.9, 1.9, and 15.9, 4.6 Hz, respectively. These data verify that the coupling had indeed taken place and that the required trans stereochemistry about the ring and the alkene remained intact.

Thermolysis of **16** in nitromethane at 90 °C for 5 h gave in 82% yield a 3:1 mixture of trans and cis tricyclic urethanes **18** and **19**. The stereochemistry of these adducts



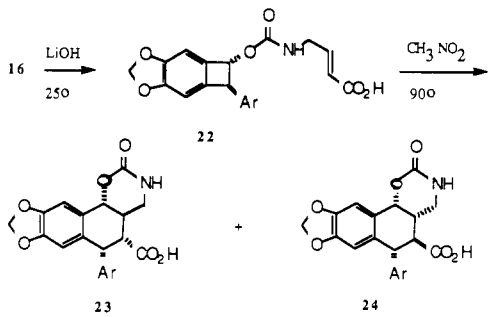
was assigned on the basis of the vicinal coupling constants between the hydrogens on the tetrahydronaphthalene ring. For isomer **19** $J_{1,2}$ and $J_{3,4}$ were 11.5 and 2.6 Hz, respectively, indicative of a trans-1,2 and a cis-3,4 relationship; the comparable data for **18** ($J_{1,2}$ = 6.0, $J_{3,4}$ = 9.9 Hz) point to a cis-1,2 and trans-3,4 stereochemical assignment. The assignment for **18** was eventually corroborated by its conversion to podophyllotoxin.

The initial plan called for the hydrolysis of both the ester and urethane functions of **18** to generate amino acid **20**,



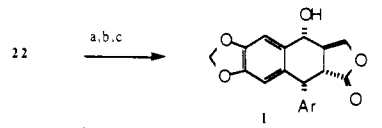
which upon diazotization was expected to yield podophyllotoxin via a reaction in which the diazonium salt was trapped by the carboxylic acid function to generate the γ-lactone. Vyas and co-workers had previously shown that the isomeric amino acid **21** gave epipodophyllotoxin (**3**) in good yield under typical diazotization conditions.[3b] When urethane ester **18** was hydrolyzed in refluxing aqueous LiOH and the resulting product diazotized with sodium nitrite in acetic acid, the product obtained was shown by 300-MHz NMR to be a 1:1 mixture of podo- and picropodophyllotoxin (**2**). The isomerization at C-2 was shown to occur prior to ester hydrolysis, with the 1:1 ratio representing the thermodynamic equilibrium between the axial and equatorial substituent at C-2 in **18**.

This isomerization could be avoided by converting the methyl ester in **16** to its acid prior to the thermolysis. Thus treatment of **16** with LiOH in aqueous THF at 25 °C gave acid **22**, mp 106–108 °C, in 86% yield. The proton NMR spectrum of **22** was quite similar to that of **17** after deletion of the methyl ester signal. Thermolysis of **22** in nitromethane at 90 °C for 5 h gave a 5:1 mixture of trans and cis acids **23** and **24**, respectively, as determined by proton NMR examination of the crude reaction mixture after treatment of the cyclization product with diazomethane, which yielded the same esters **18** and **19** obtained above.



The yield of acids in the cyclization reaction was >60% based on the ester mixture obtained as described above.

When the crude cyclization product was refluxed with 0.2 M LiOH for 0.5 h and then diazotized with sodium nitrite while the solution was buffered to pH 4 with KH_2PO_4, (±)-podophyllotoxin was isolated in 23% overall yield from methyl ester **16**. The infrared and NMR



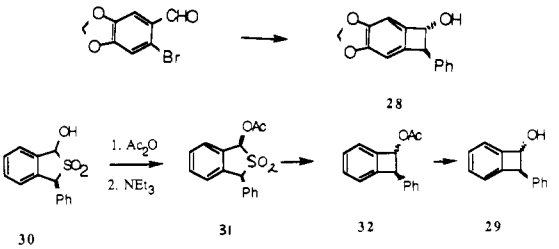
Reagents: a) D, CH_3NO_2, 90°; b)LiOH/100°; c)H^+/HNO_2

spectra of **1** thus produced were identical with those of authentic picropodophyllin and showed no trace of contamination by either picropodophyllotoxin (**2**) or epiisopodophyllotoxin (**25**).[5] Thus podophyllotoxin was obtained in six steps, including three purifications, from *trans*-2-(3,4,5-trimethoxyphenyl)-4,5-(methylenedioxy)benzocyclobutyl acetate (**13**) in 11% nonoptimized yield. The observation that **25**, the expected product from the diazotization of cis acid **24**, was not isolated as a contaminant is somewhat surprising and may be due to the alternate trapping of the diazonium salt by the cis 4-hydroxy group to form an oxetane carboxylic acid, which would be lost in the basic workup.

Podophyllotoxin Analogues

In order to demonstrate the viability of our synthesis for the preparation of podophyllotoxin analogues that might be of interest for the probing of the basis of the mechanism of action of podophyllotoxin or Etoposide, we have synthesized the analogues **26** and **27**.

The requisite benzocyclobutenol **28** needed for the preparation of **26** was prepared in a manner analogous to **7**. The overall yield of the acetate of **28** from 6-bromo-

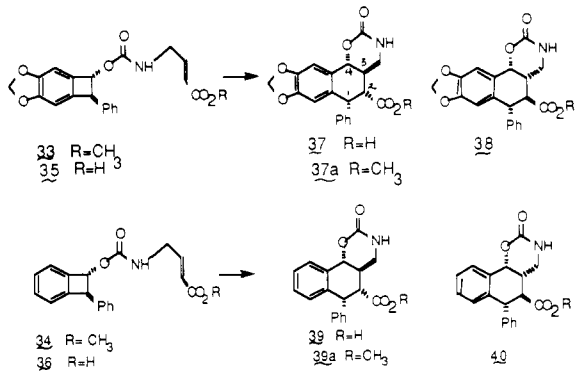


piperonal was 11%.[8] See Experimental Section for details. The parent *trans*-2-phenylbenzocyclobutanol (**29**) was prepared by an entirely different route. Acetylation of hydroxy sulfone **30**, available from the photolysis of 2-benzylbenzaldehyde in the presence of SO_2,[15] produced a 3:2 mixture of cis and trans acetates,[16] from which the cis

(15) Charlton, J. L.; Durst, T. *Tetrahedron Lett.* **1984**, *25*, 2663.
(16) Durst, T.; Kozma, E. C.; Charlton, J. L. *J. Org. Chem.* **1985**, *50*, 4829.

isomer **31** was isolated in 49% yield by fractional crystallization from benzene–hexane. It was found that the trans isomer could be isomerized to reestablish the 3:2 cis:trans ratio by treatment with triethylamine. Thus recrystallization of the acetates from hexanes in the presence of triethylamine produced essentially complete conversion of the trans isomer to the cis isomer **31** in 62% yield from benzylbenzaldehyde. Thermolysis of **31** afforded pure *trans*-2-phenylbenzocyclobutyl acetate (**32**),[17] which could be hydrolyzed in methanolic HCl at 0 °C to give the unstable *trans*-2-phenylbenzocyclobutenol (**29**).

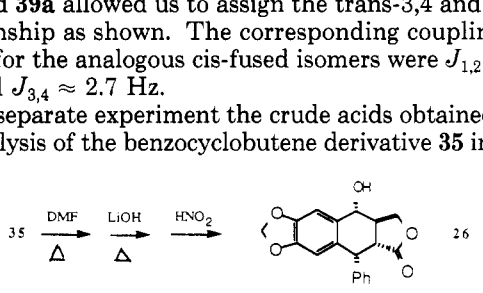
Both benzocyclobutenols **28** and **29** were coupled with isocyanate **17** in the presence of triphenyltin acetate to afford urethanes **33** and **34** in 50 and 43% yield, respectively. Both esters were subsequently hydrolyzed in 0.2



N LiOH at 25 °C and gave the corresponding acids **35** and **36** in essentially quantitative yield. Thermolysis of **35** in nitromethane at 85–90 °C for 4 h yielded a 4:1 mixture of the trans-fused and cis-fused acids **37** and **38**, from which methyl ester **37a** was isolated in 50% yield upon treatment with diazomethane. The proton NMR spectrum of **37a** showed the following signals, ascribed to the hydrogens on the tetrahydronaphthalene ring: H_1 = 4.51 (d, J = 5.9 Hz), H_2 = 3.05 (dd, J = 12.1, 5.9 Hz), H_3 = 2.63 (m), H_4 = 5.07 (d, J = 10.2 Hz). The spectroscopic properties of the cis-fused ester are recorded in the Experimental Section.

Trans-fused tricyclic ester **39a**, mp 260 °C, was similarly prepared via thermolysis of acid **35** and isolated in 27% yield along with 13% of the cis-fused analogue. The key protons H_1 and H_2 appeared at 4.65 and 5.18 ppm with $J_{1,2}$ = 5.9 Hz and $J_{3,4}$ = 10.2 Hz. The 10.2- and 5.9-Hz coupling constants for $J_{3,4}$ and $J_{1,2}$, respectively, in both **37a** and **39a** allowed us to assign the trans-3,4 and cis-1,2 relationship as shown. The corresponding coupling constants for the analogous cis-fused isomers were $J_{1,2} \approx 11.5$ Hz and $J_{3,4} \approx 2.7$ Hz.

In a separate experiment the crude acids obtained upon thermolysis of the benzocyclobutene derivative **35** in DMF



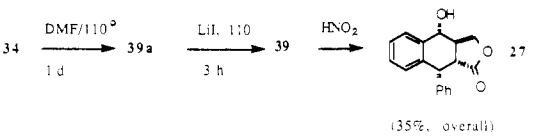
were refluxed in 0.2 N LiOH to hydrolyze the urethane function, and the resultant amino acid was diazotized at pH 4 as above. The overall yield of the podophyllotoxin analogue **26**, mp 247–248 °C, from the benzocyclobutene ester was 15%. The NMR spectrum of **26** was very similar to that of podophyllotoxin itself except for the expected differences in the chemical shifts due to the replacement of the trimethoxyaryl by a phenyl ring.

(17) Charlton, J. L.; Alauddin, M. M.; Penner, G. H. *Can. J. Chem.* **1986**, *25*, 793.

Table I. Solvent Effects on the Endo/Exo Ratio in the Thermolysis of the Esters 16, 33, and 34

ester	solvent (temp, °C)	endo/exo	yield, %
16	toluene (110)	1:1	
16	methanol (65)	2.5:1	
16	nitromethane (101)	2:1	47
33	toluene (110)	1:1	
33	nitromethane (101)	1.5:1	51
33	DMF (100)	4:1	56
34	nitromethane (100)	3:1	62

The preparation of the analogue **27** was also carried out from ester **34** without the purification on any intermediates analogous to the conversion of **22** and **33** to **1** and **26**, respectively. In this example the yield of **27** from **34** was



a very disappointing 8%. The spectroscopic properties of **27** were as expected (see Experimental Section). The yield of **27** from **34** could be improved to a more acceptable 35% via the following variation. Thus urethane ester **34** was heated for 1 day in dry DMF at 110 °C to produce a 4:1 ratio of **39a** and its cis analogue. Excess LiI was added to the solution and the mixture was heated at 110–115 °C for 3 h while nitrogen was passed over the solution to help remove the methyl iodide generated by the reaction, thus producing the acid **39**. The cyclic urethane function of **39** was removed by heating at reflux in aqueous 0.2 N LiOH for 0.5 h, and finally the amino acid thus produced was diazotized to give **27**. Presumably this variation could be used to advantage in both the preparation of podophyllotoxin and the analogue **26**.

Solvent Effects on the Exo/Endo Ratio in the Intramolecular Diels–Alder Reaction

In general, solvent effects are reputed to be rather unimportant in Diels–Alder reactions. However, in the present intramolecular version of a Diels–Alder reaction, we observed some rather dramatic changes in the exo/endo ratio when the benzocyclobutene derivatives **16**, **22**, **33**, and **34** were thermolyzed in different solvents. See Table I. Solvents such as DMF or nitromethane that have a high dielectric constant (37) gave higher endo/exo ratios (2:1 to 4:1) as compared to toluene (endo/exo ratio 1:1), which has a dielectric constant of about 2. The reaction temperatures were in the 90–110 °C range for almost all of these reactions.

Berson[18] has reported a small variation in the endo/exo ratio in the reaction of methyl crotonate with cyclopentadiene. For example, the endo/exo ratios varied from 52:48 to 56:44 to 58:42 in going from decalin to DMF to nitromethane. It was proposed by Berson that the transition state for the endo addition has a greater dipole moment than that for the exo addition and thus polar solvents should preferentially stabilize the endo transition state. Our results would seem to fit this theory. Most importantly, it should be noted that for the intramolecular reaction studied, the changes in the ratio were substantial enough to be of synthetic significance. Interestingly, where comparisons are available, the conversion of the methyl esters **16**, **33**, and **34** to the corresponding acids **22**, **35**, and **36** further improved the endo/exo ratio. Where data are available, it appears for the acids, too, that the more polar

(18) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.

solvents give higher endo/exo ratios.

Recently, Parker and Iqbal[19] noted that the ratio of trans-fused to cis-fused hydrindans obtained from several 1,3,8-nonatrienes increased by factors ranging from 1.5 to 6 when the reaction solvent was changed from toluene or benzene to *N,N*-dimethylaniline. Sternbach and Rossana[20] have also noted significant changes in the diastereomer ratios in intramolecular Diels–Alder reactions involving furan derivatives. Thus perhaps the conventional acceptance of the unimportance of solvent in intramolecular Diels–Alder reactions needs to be questioned and reexamined.

Experimental Section

Proton NMR spectra were recorded on a Varian XL-300 spectrometer in $CDCl_3$ solution. Infrared spectra were obtained on a Perkin-Elmer 783 spectrophotometer, and mass spectra were obtained on a VG7070 instrument. The MS peak intensities are given as a percent of the base peak. The usual workup involved extraction with CH_2Cl_2 or ethyl acetate, washing the organic extracts with water and then saturated NaCl solution, drying the organic extracts with anhydrous $MgSO_4$ and evaporating the solvents on a rotory evaporator. Tetrahydrofuran was distilled over sodium–benzophenone, diisopropylamine and DMF were distilled from calcium hydride, and acetonitrile was distilled from phosphorus pentoxide; all distillations were carried out under a N_2 atmosphere.

Preparation of *trans*-2-(3,4,5-Trimethoxyphenyl)benzocyclobutyl Acetate (13). To a solution of LDA (41 mmol) in 170 mL of THF at −78 °C was added 42.1 mmol (2.20 mL) of acetonitrile. After a 10-min reaction time 13.5 g (34.2 mmol) of benzophenone **9** dissolved in 125 mL of THF was added over a 10-min period. The reaction mixture was stirred for a further 10 min and then quenched with saturated NH_4Cl solution. Workup afforded 14.5 g (97%) of cyanohydrin **10** as white crystals: mp 171–172 °C (CH_2Cl_2–ether); IR 3300–3600 (m), 2257 (w) cm^{-1}; NMR δ 3.33 (d, J = 16.0 Hz, 1 H), 3.40 (d, J = 16.0 Hz, 1 H) 3.44 (s, 1 H, OH), 3.77 (s, 6 H), 3.83 (s, 3 H), 6.05 (d, J = 1.5 Hz, 1 H), 6.06 (d, J = 1.5 Hz, 1 H), 6.48 (s, 2 H), 7.01 (s, 1 H), 7.33 (s, 1 H). Anal. Calcd for $C_{19}H_{18}BrNO_6$: C, 52.31; H, 4.16. Found: C, 52.35; H, 4.31.

A solution of **10** (14.0 g, 33.5 mmol) and 1.0 g of $TsOH·H_2O$ in 250 mL of benzene was refluxed for 40 min. The reaction mixture was cooled, washed successively with saturated $NaHCO_3$ and saturated NaCl solutions, dried, and evaporated to yield 13.3 g (99%) of a cream-colored solid. The vinyl hydrogen of the product α,β-unsaturated nitrile occurred as two singlets (δ 5.44 and 5.89 (total 1 H)), indicating that two geometrical isomers were obtained. Recrystallization from ether yielded one pure isomer, mp 159–161 °C, having an infrared band at 2219 cm^{-1} and the vinyl hydrogen singlet in the NMR at δ 5.89. Anal. Calcd for $C_{19}H_{16}BrNO_5$: C, 54.56; H, 3.86. Found: C, 54.94; H, 4.13.

Magnesium turnings (8.0 g, 329 mmol) in 100 mL of methanol were activated with a few crystals of iodine at 25 °C until H_2 was rapidly evolved. The mixture was cooled to −36 °C, and a solution of 13.2 g (31.4 mmol) of the above isomeric α,β-unsaturated nitrile in 150 mL of THF was added. The reaction mixture was stirred for 2 h at −36 °C and then poured into 10% HCl solution. Extraction with ether followed by the usual workup and recrystallization from ether–CH_2Cl_2 afforded 12.0 g (91%) of the saturated nitrile as colorless prisms: mp 157 °C; IR (neat) 2248 cm^{-1}; NMR δ 2.95 (d, J = 7.4 Hz, 1 H), 3.82 (s, 3 H), 3.83 (s, 6 H), 4.75 (t, J = 7.4 Hz, 1 H), 5.96 (s, 2 H), 6.45 (s, 2 H), 6.61 (s, 1 H), 7.03 (s, 1 H). Anal. Calcd for $C_{19}H_{18}BrNO_3$: C, 54.30; H, 4.32. Found: C, 54.08; H, 4.32.

A suspension of the above nitrile (11.6 g, 24.8 mmol) in 150 mL of ethanol was saturated with HCl(g) at 25 °C. Methylene chloride (50 mL) was added, and the solution was refluxed for 1 h and then kept at 25 °C for 15 h. The solution was reduced to 100 mL, then diluted with 100 mL of ethanol and 20 mL of H_2O, and refluxed for 4 h. Finally, the cooled reaction mixture was poured into 500 mL of H_2O, and the solid product was isolated by filtration to yield, after recrystallization from ethanol, 12.0 g (93%) of **11** as colorless needles: mp 113 °C; IR 1734 (s) cm^{-1}; NMR δ 1.13 (t, J = 7.2 Hz, 3 H), 2.92 (d, J = 8.3 Hz, 2 H), 3.79 (s, 3 H) 3.80 (s, 6 H), 4.05 (q, J = 7.2 Hz, 2 H), 4.92 (t, J = 8.3 Hz, 1 H), 5.92 (d, J = 1.4 Hz, 1 H), 5.93 (d, J = 1.4 Hz, 1 H), 6.45 (s, 2 H), 6.64 (s, 1 H), 6.99 (s, 1 H). Anal. Calcd for $C_{21}H_{23}BrO_7$: C, 53.98; H, 4.96. Found: C, 53.59; H, 4.93.

Sodium amide in NH_3 was prepared by adding 1.19 g (51.8 mmol) of sodium cut in small pieces to 200 mL of liquid NH_3 at −78 °C and then at −33 °C for 10 min until the blue color had disappeared and a gray suspension had formed. The suspension was recooled to −78 °C, and 6.00 g (12.8 mmol) of bromo ester **11** dissolved in 40 mL of THF was added quickly, upon which a deep wine-colored solution was produced. After a further 10 min of reaction time 20 mL of ammonium chloride was added portionwise and the ammonia was allowed to boil off. Extractive workup with methylene chloride followed by chromatography on silica gel yielded 2.09 g (42%) of a 1:1 mixture of benzocyclobutene esters as a pale yellow foam.

A solution of 1.96 g (5.47 mmol) of the above mixture of esters in 3.0 mL of DMSO and 3.0 mL of 50% KOH was kept at 25 °C for 1 h and then carefully acidified at 0 °C with concentrated HCl. The usual extractive workup followed by recrystallization from methylene chloride–ether gave 1.54 g (85%) of **12** as white crystals: mp 145 °C; IR 1700 (s), 1730 (m), 2500–3500 (m) cm^{-1}; NMR δ 3.81 (s, 6 H), 3.82 (s, 3 H), 3.93 (d, J = 1.9 Hz, 1 H), 4.67 (d, J = 1.9 Hz, 1 H), 5.91 (d, J = 1.5 Hz, 1 H), 5.96 (d, J = 1.5 Hz, 1 H), 6.48 (s, 2 H), 6.72 (s, 1 H), 6.79 (s, 1 H); MS m/e 358 (93), 283 (100).

Acid **12** (1.53 g, 4.30 mmol) in 45 mL of THF and 10 mL of acetic acid at 18 °C was allowed to react with 2.10 g of 90% $Pb(OAc)_4$. The solution was stirred for 1 h, during which time a heavy white precipitate formed. The usual workup (ether) followed by silica gel chromatography furnished 1.15 g (76%) of benzocyclobutyl acetate **13** as white crystals, mp 134–135 °C, from ether: IR 1735 (s) cm^{-1}; NMR δ 2.12 (s, 3 H), 3.81 (s, 6 H), 3.82 (s, 3 H), 4.38 (d, J = 1.8 Hz, 1 H), 5.45 (d, J = 1.8 Hz, 1 H), 5.93 (d, J = 2.0 Hz, 1 H), 5.96 (d, J = 2.0 Hz, 1 H), 6.45 (s, 2 H), 6.70 (s, 1 H), 6.83 (s, 1 H). Anal. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.81; H, 5.55.

Isocyanate 17. Phosgene was bubbled through a suspension of 2.90 g (19.2 mmol) of methyl *trans*-4-aminocrotonate hydrochloride (**13**) in 100 mL of refluxing chlorobenzene. Evaporation of the chlorobenzene and distillation of the residue gave 1.59 g (57%) of **17**: bp 65 °C/0.075 mm; IR 2257 (vs), 1725 (s) cm^{-1}; NMR 3.74 (s, 3 H), 4.13 (dd, J = 4.3, 2.1 Hz, 2 H), 6.10 (dt, J = 15.4, 2.1 Hz, 1 H), 6.88 (dt, J = 15.4, 4.3 Hz, 1 H); MS m/e 141 (15), 100 (81), 98 (38), 86 (100), 82 (75).

Coupling of 17 with 7. Preparation of 16. A solution of 168 mg (0.45 mmol) of **13** in 2 mL of CH_2Cl_2 was added at −10 °C to a mixture of 4.0 mL of methanol and 1.0 mL of acetyl chloride. The reaction mixture was kept at −10 °C for 4 h, diluted with 10 mL of CH_2Cl_2, and washed with H_2O until the pH was neutral.

The organic extract was then diluted with carbon tetrachloride (10 mL), and the solution was reduced to 5 mL without letting the temperature rise above 0 °C. This dilution–evaporation procedure was repeated. To the solution thus obtained were added 5 mL of CH_2Cl_2 at 0 °C, 72 mg of isocyanate **17**, and 25 mg (0.062 mmol) of triphenyltin acetate. The solvent was then evaporated to yield a viscous oil, which was allowed to warm to 25 °C. The oil was then purified on silica gel to afford 104 mg (47%) of the coupled urethane ester **16**: mp 141–142 °C; NMR δ 3.72 (s, 3 H), 3.80 (3, 6 H), 3.81 (s, 3 H), 4.00 (m, 2 H), 4.36 (d, J = 0.6 Hz, 1 H), 4.90 (m, NH), 5.47 (d, J = 0.6 Hz, 1 H), 5.93 (d, J = 1.3 Hz, 1 H), 5.95 (d, J = 1.3 Hz, 1 H), 5.96 (dt, J = 15.9 , 1.9 Hz, 1 H), 6.45 (s, 2 H), 6.70 (s, 1 H), 6.85 (s, 1 H), 6.92 (dt, J = 15.9 , 4.6 Hz, 1 H); MS m/e 471 ($M^{\cdot+}$, 58), 312 (100).

The NMR spectrum of the crude benzocyclobutenol **7** showed peaks at δ 3.80 (s, 6 H), 3.82 (s, 3 H), 4.17 (s, 1 H), 4.77 (bs, 2 H), 5.93 (d, J = 2.0 Hz, 1 H), 5.96 (d, J = 2.0 Hz, 1 H), 6.40 (s, 2 H), 6.71 (s, 1 H), 6.48 (s, 1 H).

Thermolysis of 16. A solution of 51.2 mg (0.109 mmol) of **16** in 5 mL of nitromethane was refluxed for 1.5 h. The solvent was evaporated, and the product was purified by plate chromatography

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to yield 31.9 mg (62%) of **18** as colorless cubes (mp 272 °C) and 10.1 mg (20%) of **19** as white needles (mp 234 °C). Compound **18** showed infrared peaks at 1712 (vs), 1735 (s), and 3385 (m) cm^{-1} and had NMR peaks at δ 2.64 (m, 1 H), 3.03 (m, 2 H), 3.56 (s, 3 H), 3.72 (s, 6 H), 3.78 (s, 3 H), 3.74 (m, 1 H), 4.44 (d, J = 6.0 Hz, 1 H), 5.05 (d, J = 9.9 Hz, 1 H), 5.14 (m, 1 H), 5.92 (d, J = 1.3 Hz, 1 H), 5.94 (d, J = 1.3 Hz, 1 H), 6.12 (s, 2 H), 6.37 (s, 1 H), 7.15 (s, 1 H). HRMS calcd for $C_{24}H_{25}NO_4$, 471.1527; found, 471.1527. Anal. Calcd for $C_{24}H_{25}NO_4$: C, 61.14; H, 5.34. Found: C, 61.18; H, 5.58.

The cis-fused compound **19** showed broad absorption at 1700–1740 cm^{-1} and at 3300 and 3400 cm^{-1} in the infrared. NMR peaks were at δ 2.58 (m, 1 H), 3.12 (dd, J = 12.5, 4.0 Hz, 1 H), 3.21 (t, 12.0 Hz, 1 H), 3.51 (s, 3 H), 3.64 (dd, J = 12.5, 5.0 Hz, 1 H), 3.77 (s, 6 H), 3.83 (s, 3 H), 4.14 (d, J = 11.5 Hz, 1 H), 5.28 (d, J = 2.7 Hz, 1 H), 5.91 (d, J = 1.3 Hz, 1 H), 5.92 (d, J = 1.3 Hz, 1 H), 6.28 (s, 1 H), 6.30 (s, 2 H), 6.82 (s, 1 H).

Hydrolysis of 16 to 22. Ester **16** (62.2 mg, 0.132 mmol) was dissolved in a mixture prepared by mixing 0.2 mL of 2 M LiOH, 2 mL of water, and 10 mL of THF at 25 °C. The biphasic system was stirred for 3.5 h. The THF was then evaporated under reduced pressure, and the reaction mixture was acidified with 10% HCl. The usual extractive workup followed by recrystallization from CH_2Cl_2–hexanes yielded 52.1 mg (86%) of acid **22** as a white solid: mp 106–108 °C; IR 2900–3400 (m), 1690–1720 (s) cm^{-1}; NMR 3.80 (s, 6 H), 3.81 (3 H), 4.04 (m, 2 H), 4.37 (m, 1 H), 4.96 (m, NH), 5.48 (s, 1 H), 5.94 (d, J = 1.3 Hz, 1 H), 5.96 (d, J = 1.3 Hz, 1 H), 5.97 (dt, J = 15.6, 1.7 Hz, 1 H), 6.46 (s, 2 H), 6.71 (s, 1 H), 6.86 (s, 1 H), 7.02 (dt, J = 15.6, 4.8 Hz, 1 H); MS m/e 457 (40), 312 (100).

Thermolysis of Acid 22. A solution of 10.0 mg of acid **22** in 10 mL of nitromethane was heated at 90 °C for 5 h. The nitromethane was evaporated, and the residue was suspended in 10 mL of CH_2Cl_2. Excess diazomethane in ether was added, and the volatile components were evaporated. A 300-MHz spectrum of the total crude product indicated a 5:1 mixture of tricyclic ester **18** and **19**. The crude product was recrystallized from methanol and gave 5.0 mg (50%) of pure **18**.

Preparation of Podophyllotoxin from 16. Ester **16** (14.1 mg, 0.030 mmol) was hydrolyzed as above, and the crude product was heated in 15 mL of nitromethane at 90 °C for 5 h. The residue obtained upon evaporation of the nitromethane was heated at reflux in 10 mL of 0.2 M LiOH. The resulting cooled solution was acidified with 10% HCl, buffered to pH 4 with 0.2 M KH_2PO_4, and cooled to 0 °C. Sodium nitrite (0.3 g, 3.5 mmol) was added followed by 10% HCl to give pH 4. The solution was then stirred for 18 h and a tan precipitate was produced. Extractive workup followed by plate chromatography (10:1 methylene chloride–acetone) yielded 2.8 mg (23%) of pure (±)-podophyllotoxin as white crystals, mp 236–237 °C. The NMR and infrared spectra of the product were virtually identical with those of an authentic sample.

Preparation of Benzocyclobutenol 28. 6-Bromopiperonal (60.0 g, 0.26 mol), diethyl malonate (42.0 g, 0.26 mol), and 2.6 mL of piperidine were dissolved in 100 mL of toluene and refluxed for 48 h with removal of water. Workup and recrystallization of the product from ethanol–water yielded 71.5 g (74%) of the expected unsaturated diester, mp 50–52 °C.

A solution of 90 g (0.242 mol) of the above ester in 450 mL of ether and 180 mL of benzene at −78 °C was allowed to react with phenylmagnesium bromide in 150 mL of ether prepared from 33.2 mL (0.315 mol) of bromobenzene. The mixture was allowed to warm slowly to 25 °C and produced a deep yellow solution, which was quenched with saturated ammonium chloride. Further workup afforded 108.9 g (100%) of the desired addition product as a pale yellow oil: IR 1735 (s) cm^{-1}; NMR δ 1.00 (t, J = 7.5 Hz, 3 H), 1.09 (t, J = 7.5 Hz, 3 H), 3.98 (dq, J = 7.5, 1.1 Hz, 2 H), 4.05 (q, J = 7.5 Hz, 2 H), 4.21 (d, J = 13.2 Hz, 1 H), 5.26 (d, J = 13.2 Hz, 1 H), 5.89 (d, J = 2 Hz, 1 H), 5.93 (d, J = 2 Hz, 1 H), 6.86 (s, 1 H), 6.96 (s, 1 H), 7.1–7.3 (m, 5 H).

The above diester was hydrolyzed and decarboxylated to afford in 61% yield 2-(2-bromo-3,4-(methylenedioxy)phenyl)-2-phenylpropionic acid: mp 190–192 °C; IR 2500–3600 (broad), and 1709 (s) cm^{-1}; NMR δ 3.00 (d, J = 8.6 Hz, 1 H), 3.01 (d, J = 8.6 Hz, 1 H), 4.98 (t, J = 8.6 Hz, 1 H), 5.90 (d, J = 2 Hz, 1 H), 5.93 (d, J = 2 Hz, 1 H, 6.65 (s, 1 H), 6.99 (s, 1 H), 7.1–7.3 (m, 5 H). Anal. Calcd for $C_{16}H_{13}BrO_4$: C, 55.04; H, 3.75. Found: C, 54.62; H, 4.03.

The above acid was esterified in ethanol with $TsOH·H_2O$ as catalyst, and the resulting ester (25 g, 66.3 mmol) dissolved in 90 mL of THF was added in 1 min to a solution of $NaHH_2$ (6.10 g of Na) in 700 mL of NH_3 at −78 °C. The resulting solution was stirred for an additional 8 min and quenched by portionwise addition of 50 g of NH_4Cl. Usual workup afforded 7.13 g (36%) of a 1:1 mixture of substituted cis- and trans-2-phenyl-4,5-(methylenedioxy)benzocyclobutene-1-carboxylic acid esters.

These esters (11.2 g) were dissolved in 30 of DMSO and 30 mL of 50% NaOH, and the solution was stirred for 4 h, diluted with 300 mL of H_2O, acidified, and extracted. Purification of the product by recrystallization from CH_2Cl_2–hexane gave 8.14 g of 80% *trans*-2-phenyl-4,5-(methylenedioxy)benzocyclobutene-1-carboxylic acid, mp 140 °C (dec). The NMR spectrum showed peaks at δ 3.93 (d, J = 2.6 Hz, 1 H), 4.75 (d, J = 2.6 Hz, 1 H), 5.90 (d, J = 1.6 Hz, 1 H), 5.93 (d, J = 1.6 Hz, 1 H), 6.73 (s, 1 H), 6.78 (s, 1 H), 7.1–7.4 (m, 5 H). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.69; H, 4.95.

Preparation of the Acetate of 28. To a solution of 7.20 g (26.8 mmol) of the above acid dissolved in 250 mL of THF at 18 °C was added 12.9 g (26.6 mmol) of $Pb(OAc)_4$ (90%). The reaction mixture was stirred for 1 h, during which time a heavy white precipitate formed. The usual extractive workup, followed by silica gel chromatography afforded 4.09 g (54%) of the pure acetate of **28**, mp 83–84 °C. The estimated crude yield of acetate was 90%. IR 1740 cm^{-1}; NMR δ 2.12 (s, 3 H), 4.46 (s, 1 H), 5.45 (s, 1 H), 5.94 (s, 2 H), 6.69 (s, 1 H), 6.83 (s, 1 H), 7.2–7.3 (m, 5 H). Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.06; H, 4.91.

Coupling of Benzocyclobutenol 28 with Isocyanate 17. The hydrolysis of the acetate of **28** to **28** was carried out for 3 h at 0 °C on 3.03 g of acetate in 30 mL of CH_2Cl_2 and 60 mL of methanol to which had been added 15 mL of acetyl chloride. Workup similar to the preparation of **7** afforded a CCl_4 solution of **28**: NMR δ 2.30 (d, J = 7.7 Hz, OH), 4.25 (s, 1 H), 4.80 (d, J = 7.7 Hz, 1 H), 5.93 (s, 2 H), 6.70 (s, 1 H), 6.83 (s, 1 H), 7.1–7.3 (m, 5 H). This solution was diluted with 100 mL of CH_2Cl_2 and allowed to react with 1.52 g (10.8 mmol) of isocyanate **17** and 0.40 g (1 mmol) of triphenyltin acetate at 0 °C. After the mixing was complete, the solvent was evaporated to yield a viscous oil from which 2.06 g (50%) of the coupled urethane ester **33**, mp 110–111 °C, was obtained. IR (neat) 3300–3460 (m), 1723 (s) cm^{-1}; NMR δ 3.72 (s, 3 H), 4.01 (m, 2 H), 4.44 (s, 1 H), 4.9 (br, NH), 5.46 (s, 1 H), 5.93 (s, 2 H), 5.96 (dt, J = 16, 1.9 Hz, 1 H), 6.70 (s, 1 H), 6.85 (s, 1 H), 6.92 (dt, J = 16, 5.0 Hz, 1 H), 7.1–7.3 (m, 5 H).

Hydrolysis of 33. Preparation of 35. Ester **33** (1.65 g, 4.33 mmol) was added to 100 mL of THF, 20 mL of H_2O, and 5 mL of 2 M LiOH. The biphasic system was stirred at 23 °C for 7 h, acidified with 10% HCl, and extracted with CH_2Cl_2. The yield of crude acid **35** was 1.52 g (96%): mp 156–157 °C; IR 2400–3600 (b), 1690 (s) cm^{-1}; NMR δ 4.04 (m, 2 H), 4.44 (s, 1 H), 4.94 (NH), 5.47 (s, 1 H), 5.93 (s, 2 H), 5.97 (dt, J = 15.9, 1.8 Hz, 1 H), 6.70 (s, 1 H), 6.85 (s, 1 H), 7.01 (dt, J = 15.9, 5 Hz, 1 H), 7.2–7.3 (m, 5 H).

Thermolysis of 33. A solution of 64 mg (0.17 mmol) of ester **33** was heated in 5 mL of nitromethane at 86 °C for 4 h. Evaporation of the solvent followed by crystallization from CH_2Cl_2 and plate chromatography afforded 30 mg (47%) of the trans-fused tricyclic ester **37a** and 20 mg (31%) of the cis-fused product **38**. A 300-MHz NMR spectrum of the total crude product indicated a 2:1 ratio of **37a** to **38a**.

The trans-fused ester, mp 300–302 °C, had infrared peaks (KBr) at 3300–3500 (m) and 1715 (s) cm^{-1}; NMR δ 2.63 (m, 1 H), 3.02 (t, J = 11.0 Hz, 1 H), 3.05 (dd, J = 12.2, 5.9 Hz, 1 H), 3.53 (s, 3 H), 3.72 (ddd, J = 11.0, 5.4, 4.4 Hz, 1 H), 4.51 (d, J = 5.9 Hz, 1 H), 5.07 (d, J = 10.2 Hz, 1 H), 5.15 (m, NH), 5.90 (d, J = 1.3 Hz, 1 H), 5.91 (d, J = 1.3 Hz, 1 H), 6.33 (s, 1 H), 6.9–7.0 (m, 2 H), 7.16 (s, 1 H), 7.2–7.3 (m, 3 H). Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.15; H, 5.02. Found C, 66.00; H, 5.37.

The cis-fused ester, mp 230–231 °C, had IR peaks at 3300–3600 (s) and 1700–1750 (s) cm^{-1} when taken in a KBr pellet. Its NMR spectrum showed peaks at δ 2.61 (m, 1 H), 3.12 (ddd, J = 12.6, 4.3, 1.4 Hz, 1 H), 3.23 (t, J = 11.8 Hz, 1 H), 3.47 (s, 3 H), 3.68 (dd, J = 12.5, 4.8 Hz, 1 H), 4.22 (d, J = 11.2 Hz, 1 H), 5.29 (d,

J = 2.8 Hz, 1 H), 5.14 (m, NH), 5.88 (d, J = 1.3 Hz, 1 H), 5.90 (d, J = 1.3 Hz, 1 H), 6.20 (s, 1 H), 6.82 (s, 1 H), 7.1–7.3 (m, 5 H); MS $M^{\bullet+}$ calcd, 381; found, 381 (17).

Thermolysis of Acid 35. A solution of 3.8 mg (0.010 mmol) of acid **35** was heated in 2 mL of nitromethane for 4 h at 85–90 °C. The nitromethane was evaporated, and the residue was treated with excess diazomethane. An NMR spectrum of the total crude esters indicated a 5:1 ratio of **37a** to **38**. The yield of **37a** after plate chromatography was 51%.

Preparation of Podophyllotoxin Analogue 26 from 33. Crude acid **35**, obtained by hydrolysis of 1.65 g of **33** as described above, was heated for 5.5 h in 120 mL of nitromethane at 85–90 °C. The nitromethane was evaporated, and the residue was refluxed in aqueous LiOH (0.2 M, 200 mL) for 0.5 h. To the cooled reaction mixture were added 8 g of $KHPO_4$, 0.4 g of $NaNO_2$, and about 60 mL of 10% HCl to give a pH of approximately 4. The solution was stirred for 20 h and extracted with CH_2Cl_2. The crude product was purified by chromatography on silica gel and recrystallization from CH_2Cl_2–hexane to give 207 mg (15%) of **26** as white plates: mp 247–248 °C; IR (KBr) 3400 (s) 1760 (s) cm^{-1}; NMR δ 2.76 (m, 1 H), 2.86 (dd, J = 14.3, 4.8 Hz, 1 H), 4.08 (t, J = 9.4 Hz, 1 H), 4.57 (dd, J = 8.9, 7.1 Hz, 1 H), 4.63 (d, J = 4.8 Hz, 1 H), 4.76 (d, J = 9.2, 1 H), 5.94 (d, 2 H), 6.44 (s, 1 H), 7.1–7.3 (m, 6 H). Anal. Calcd for $C_{19}H_{16}O_3$: C, 70.36; H, 4.97. Found: C, 70.65; H, 5.36.

Preparation of Urethane 34. A solution of 0.405 g (1.70 mmol) of benzocyclobutyl acetate **32** dissolved in 10 mL of CH_2Cl_2 was added to 8 mL of methanol and 2 mL acetyl chloride at −5 °C. The reaction mixture was stirred for 5 h and then worked up as before for **7** to afford a carbon tetrachloride solution of the alcohol **29** [NMR δ 4.10 (s, 1 H), 4.96 (s, br, 2 H), 7.0–7.6 (m, 9 H); IR 3300–3500 cm^{-1}].

To the above solution of **29** were added 10 mL of methylene chloride, 0.237 g (1.68 mmol) of isocyanate **17**, and 85 mg of triphenyltin acetate. The solvent was evaporated at 0 °C on a rotary evaporator to produce a viscous oil, which was allowed to warm to room temperature. The crude product was purified on silica gel and gave 0.245 g (43%) of **34**: mp 93–94 °C; IR 1700–1730 (s), 3340 (m) cm^{-1}; NMR δ 3.73 (m, 3 H), 4.03 (m, 2 H), 4.64 (s, 1 H), 4.93 (m, NH), 5.67 (d, J = 1.4 Hz, 1 H), 5.97 (dt, J = 16.0, 2.0 Hz, 1 H), 6.93 (dt, J = 16.0, 4.9 Hz, 1 H), 7.2–7.6 (m, 9 H).

Preparation of Podophyllotoxin Analogue 27 from 34. A solution of 125 mg (0.371 mmol) of **34** was heated in DMF at 110 °C for 1 day. The DMF was evaporated to 2 mL, and 1.2 g (9.0 mmol) of LiI was added. The resulting solution was heated at 115 °C for 3 h while N_2 was passed over the surface of the solution. The reaction mixture was then cooled and added to 15 mL of 1% HCl. Extractive workup with ethyl acetate afforded a tan solid, which was refluxed in 75 mL of 0.2 M LiOH for 0.5 h. The solution was again cooled to 23 °C, and KH_2PO_4 (6 g), $NaNO_2$ (3 g), and 15 mL of 10% HCl were added. This solution was stirred for 20 h and then extracted with methylene chloride. The analogue **27** was obtained in 35% yield (36 mg) as white plates from methylene chloride–hexane after an initial silica gel chromatography: mp 226–227 °C; IR (KBr) 3420 (s), 1756 (s) cm^{-1}; NMR 2.06 (O-H), 2.85 (m, 1 H), 2.89 (dd, J = 14.2, 5 Hz, 1 H), 4.11 (t, J = 10.0 Hz, 1 H), 4.60 (dd, J = 9.3, 6.5 Hz, 1 H), 4.77 (d, J = 4.3 Hz, 1 H), 4.88 (d, J = 8.8 Hz, 1 H), 7.0–7.7 (m, 9 H). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.95; H, 5.85.

Thermolysis of 34. Preparation of 39a. A solution of 26.8 mg of **34** in 4 mL of DMF was heated to 110 °C for 1 day. The DMF was evaporated, and the product was separated by recrystallization and plate chromatography to give 15 mg (56%) of the trans-fused ester **39a** and 3 mg (11%) of the cis-fused analogue **40**. An NMR spectrum of the total crude reaction mixture indicated a 4:1 ratio of **39a**:**40**. Compound **39a** (mp 260 °C) had IR peaks at 1706 (s), 1728 (m), and 3420 (s) cm^{-1}; NMR peaks were at δ 2.70 (m, 1 H), 3.06 (t, J = 10.9 Hz, 1 H), 3.10 (dd, J = 10.9, 6.0 Hz, 1 H), 3.54 (s, 3 H), 3.75 (quintet, J = 5.2 Hz, 1 H), 4.65 (d, J = 5.8 Hz, 1 H), 5.11 (d, J = 3.9 Hz, NH), 5.18 (d, J = 10.2 Hz, 1 H), 6.9–7.8 (m, 9 H). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68. Found: C, 71.25; H, 5.65.

The cis analogue **40** had the following NMR data: δ 2.66 (m, 1 H), 3.15 (ddd, J = 2, 4, 12 Hz, 1 H), 3.29 (t, 12.2 Hz, 1 H), 3.48 (s, 3 H), 3.70 (dd, J = 12.7, 4.9 Hz, 1 H), 4.34 (d, J = 11.2 Hz, 1 H), 5.27 (m, NH), 5.40 (d, J = 2.5 Hz, 1 H), 6.7–7.4 (m, 9 H).

Rearrangement Approaches to Cyclic Skeletons. 6. Total Synthesis of (±)-Ptilocaulin on the Basis of Formal Bridgehead Substitution and Photochemical [1,3] Acyl Migration of a Bicyclo[3.2.2]non-6-en-2-one System[1]

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The total synthesis of (±)-ptilocaulin (1), the antimicrobial and cytotoxic guanidine-containing natural product, starting from 1-methoxybicyclo[3.2.2]non-6-en-2-one (3) is reported. The 3-*endo*-methyl derivative of **3**, **4**, was obtained selectively under kinetically controlled conditions. The bridgehead methoxy group of **4** was replaced by a butyl group, with inversion of absolute configuration, upon successive treatment with butyllithium and *p*-toluenesulfonic acid in benzene. The thus obtained 1-butyl-*exo*-8-methylbicyclo[3.2.2]non-6-en-2-one was transformed photochemically into the [5,6] fused-ring ketone, 4-butyl-*exo*-3-methylbicyclo[4.3.0]non-4-en-7-one (**7**). Transposition of the carbonyl group and the olefin of **7** to give a mixture of *exo*-3- and *endo*-3-butyl-4-*exo*-methylbicyclo[4.3.0]non-9-en-2-ones was achieved in a six-step sequence. From these conjugated ketones, (±)-ptilocaulin was derived by treatment with guanidine.

Ptilocaulin (1) is an antimicrobial and cytotoxic cyclic guanidine derivative isolated from the Caribbean sponge *Ptilocaulis* aff. *P. spiculifer* (Lamarck, 1814) by Rinehart and co-workers.[3] Because of these activities and the unusual structure, **1** is a significant synthetic target.[4-6] The absolute stereochemistry of natural (+)-ptilocaulin was

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