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# An Asymmetric Synthesis of Aza Analogues of the Tricyclic Skeleton of Daphnane and the ABC Ring System of Phorbol

Charles M. Marson,*,† Jennifer H. Pink, and David Hall

*Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, U.K.*

Michael B. Hursthouse

*Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, U.K.*

Abdul Malik

*Department of Chemistry, University of Wales, P.O. Box 912, Park Place, Cardiff CF1 3TB, U.K.*

Christopher Smith

*Rhône-Poulenc Rorer Ltd., Rainham Road South, Dagenham, Essex RM10 7XS, U.K.*

*c.m.marson@ucl.ac.uk*

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An asymmetric synthesis of aza analogues of the ABC ring system of phorbol and related compounds containing the 5−7−6-fused framework of daphnane involved construction of the central seven-membered ring by a regioselective reduction of a chiral imide and cyclization with trifluoromethanesulfonic acid. Subsequent demethylation and oxidative dearomatization of ring C afforded an enantiopure dienone **20** with the same relative and absolute configuration at the 9- and 10-positions of the phorbol skeleton.

The construction of angularly fused 5−7−6-tricyclic systems[1,2] in a stereocontrolled manner is an important challenge, in view of the variety of biologically active compounds incorporating that skeleton. For example, phorbol **1** (Figure 1) is extensively used in studies of tumor promotion and for its ability to activate protein kinase C.[3] The related 5−7−6 daphnane skeleton[2] is exemplified by the antileukemic agent gnidilatin **2**[4] and by the irritant resiniferatoxin, which also possesses analgesic properties.[5] Aconitine **3** (X = CH), representative of another set of complex carbocyclic systems, the aconite alkaloids,[6] notable for their cardiotonic and sedative properties, also contains a 5−7−6-tricyclic core. Those examples and the antileukemic activity of the *Cephalotaxus* alkaloids,[7] e.g., cephalotaxine **4**, suggested that a general route to 5−7−6 fused systems that are either carbocyclic or incorporate one nitrogen atom in the

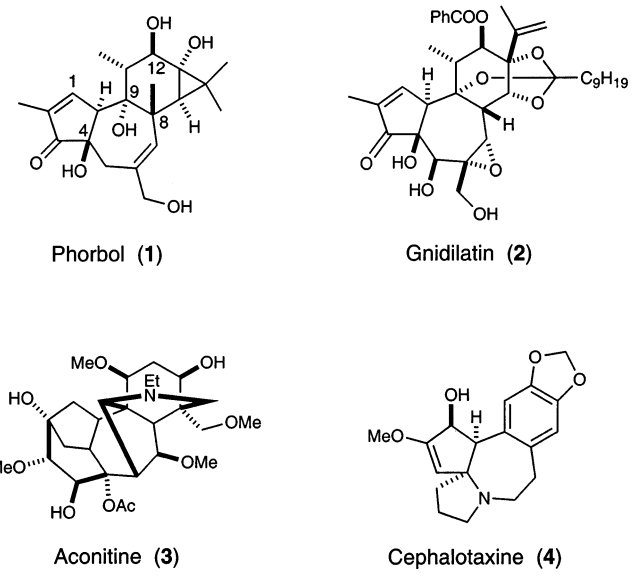


**FIGURE 1.**

† Current address: Department of Chemistry, University College London, Christopher Ingold Laboratories, 20 Gordon Street, London WC1H 0AJ, U.K.

(1) (a) Marson, C. M.; Benzies, D. W. M.; Hobson, A. D.; Adams, H.; Bailey, N. A. *J. Chem. Soc., Chem. Commun.* **1990**, 1516. (b) Marson, C. M.; Harper, S.; Walker, A. J.; Pickering, J.; Campbell, J.; Wrigglesworth, R.; Edge, S. J. *Tetrahedron* **1993**, *45*, 10339.

(2) Evans, F. J.; Taylor, S. E. *Prog. Chem. Org. Nat. Prod.* **1983**, *44*, 27.

(3) (a) Jeffrey, A. M.; Liskamp, R. M. J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 241. (b) Wender, P. A.; Koehler, K. F.; Sharkey, N. A.; Dell' Aquila, M. L.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4214. (c) Wender, P. A.; Cribbs, C. M.; Koehler, K. F.; Sharkey, N. A.; Herald, C. L.; Kamano, Y.; Pettit, G. R.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7197. (d) For a review on protein kinase C in tumor production, see: Nishizuka, Y. *Nature* **1984**, *308*, 693.

(4) Kupchan, S. M.; Shizuri, Y.; Sumner, W. C., Jr.; Haynes, H. R.; Leighton, A. P.; Sickles, B. R. *J. Org. Chem.* **1976**, *41*, 3850.

(5) Adolf, A.; Sorg, B.; Hergenhahn, M.; Hecker, E. *J. Nat. Prod.* **1982**, *45*, 347.

(6) (a) Benn, M. H.; Jacyno, J. M. In *Alkaloids−Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Vol. 1, 153. (b) Wiesner, K. *Pure Appl. Chem.* **1979**, *51*, 689.

(7) Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158.

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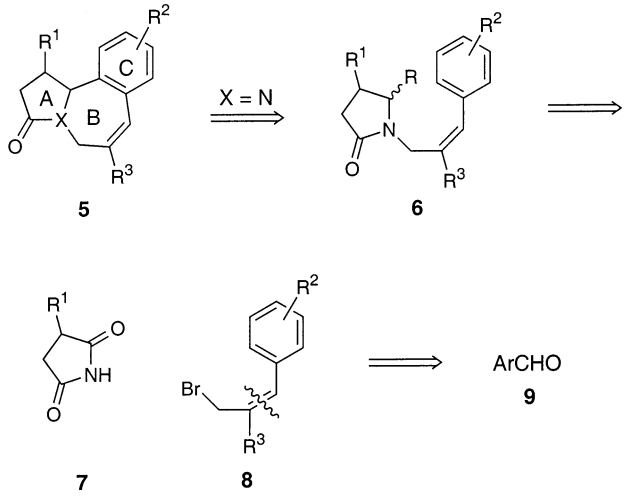
**SCHEME 1**




ring system would be useful, especially since it could also provide access to the hitherto unknown aza analogues;[8] the antimicrobial and antiparasitic bengamides incorporate a perhydroazepine ring.[9]To that end, we describe here enantioselective syntheses of the first aza analogues[10] containing the 5−7−6-fused ring system of the daphnane diterpenoids and the aconite alkaloids, together substantial functionality that is central to biological activity.

A convergent strategy was envisaged (Scheme 1) in which an intramolecular cyclization would form the central seven-membered ring. Additionally, the location of the nitrogen atom should facilitate the synthesis, stereocontrol, and potential pharmacological activity of the resulting 5−7−6 prototypes. Selection of X = N in **5** permits consideration of an acyliminium cationic cyclization[11] of **6**, which, if containing a moderately activated benzene ring, would act as an effective $\pi$-nucleophile. Construction of **6** would proceed by N-alkylation of a lactam **7** using an allylic electrophile such as **8**, which must be constructed with the required alkene configuration. It was sought to achieve control of configuration by rendering $R^2$ in **8** electron deficient, so that stereoelectronic factors would favor $R^2$ being trans to the conjugated aromatic ring.

In a Baylis−Hillman reaction,[12] 3-methoxybenzaldehyde (**10**) was reacted with methyl acrylate using 3-hydroxyquinuclidine as the catalyst to give alcohol **11** (91%, Scheme 2).[13] It was anticipated that $S_N2'$ attack upon the allylic alcohol **11** would lead to an unsaturated ester of the desired configuration. Indeed, treatment of the alcohol **11** with aqueous 48% HBr (16 h, 20 °C) furnished the allylic bromide **12** (80%) as an oil.[13] As a model study, N-alkylation of succinimide[14] with bromide **12** ($K_2CO_3$, DMF) proceeded smoothly to give the imide **13** in 80% yield. Attempted reduction of **13** with sodium borohydride[15] gave a complex mixture, $^1$H NMR spectra indicated that over-reduction had taken place, probably involving the allylic ester moiety. Reduction at lower temperature (−15 °C) proceeded slowly and was incomplete.

(3*S*)-3-Acetoxysuccinimide (**15**) was next selected as a more functionalized precursor of the $\gamma$-lactam ring; following N-alkylation[16] and subsequent regioselective reduction,[16−18] a stereoselective cyclization controlled by the absolute configuration of the acyloxy carbon atom was envisaged. The succinimide **15** was prepared[17] by successive treatment of (*S*)-malic acid with acetyl chloride, ammonia, and acetyl chloride (overall yield 50%). The succinimide **15** was alkylated with the bromide **12** (1.0 equiv) using $K_2CO_3$ (1.0 equiv) in DMF at 20 °C over 2.5 h, furnishing the imide **16** in 62% yield.

Reduction[17] of imide **16** with sodium borohydride in methanol at −8 °C over 20 min gave a 2.5:1 ratio of epimers **17** (87%). The major diastereoisomer was assigned as the (4*S*,5*S*)-cis-isomer, consistent with literature precedent.[16a] The amide **17** (without recrystallization) was treated with 5% $CF_3SO_3H$[18] in dichloromethane (75 min, 20 °C), quenched with saturated aqueous sodium hydrogen carbonate, and subjected to column chromatography which gave a 3:1 mixture (70%) of **18** and its 10-methoxy regioisomer **21**.[19] Recrystallization (twice from ethyl acetate) of the 3:1 mixture afforded the pure isomer **18**, of the absolute configuration depicted. Other isomeric lactams such as **22** and **23** may have been present in trace amounts, but they were not isolated.

The viability of functionalizing ring C of the ether **18** was tested by demethylation at position-8 using boron tribromide; that gave, in 70% yield, the corresponding phenol **19**, which was oxidatively hydroxylated using [bis-(trifluoroacetoxy)iodo]benzene[20] to give the dienone **20** as the only isolable compound. Under the reaction conditions, extensive polar material was obtained that did not elute and could not be identified. Side products generated by elimination of oxygenated functionality from **20** may have been significant. *An X-ray crystallographic determination on a single crystal of dienone* **20** *(recrystallized from propan-2-ol and 40−60 °C petroleum ether) confirmed the relative configuration as 10a*$\alpha$*, 10b*$\alpha$*, corre-*

(8) For a total synthesis of racemic phorbol skillfully executed in some 50 steps, see: (a) Wender, P. A.; Kogan, H.; Lee, H. Y.; Munger, D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957. For formal asymmetric syntheses of phorbol see: (b) Wemder, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897. (c) Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590.

(9) Quiñoa, E.; Adamczeski, M.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4494.

(10) A preliminary communication of part of this work is described in: Marson, C. M.; Pink, J. H.; Smith, C. *Tetrahedron Lett.* **1995**, *36*, 8107.

(11) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(12) (a) Baylis, A. B.; Hillman, M. E. D. *Chem. Abstr.* **1972**, *77*, 34174q. (b) Drewes S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

(13) For related $S_N2'$ displacements see: Ameer, F.; Drewes, S. E.; Neville, D.; Kaye, P. T.; Mann, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2293.

(14) Neuberger, A.; Scott, J. J. *J. Chem. Soc.* **1954**, 1820.

(15) (a) Hubert, J. C.; Steege, W.; Speckamp, W. N.; Huisman, H. O. *Synth. Commun.* **1971**, *1*, 103. (b) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(16) (a) Wijnberg, J. B. P. A.; Shoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179. (b) Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135 (c) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959.

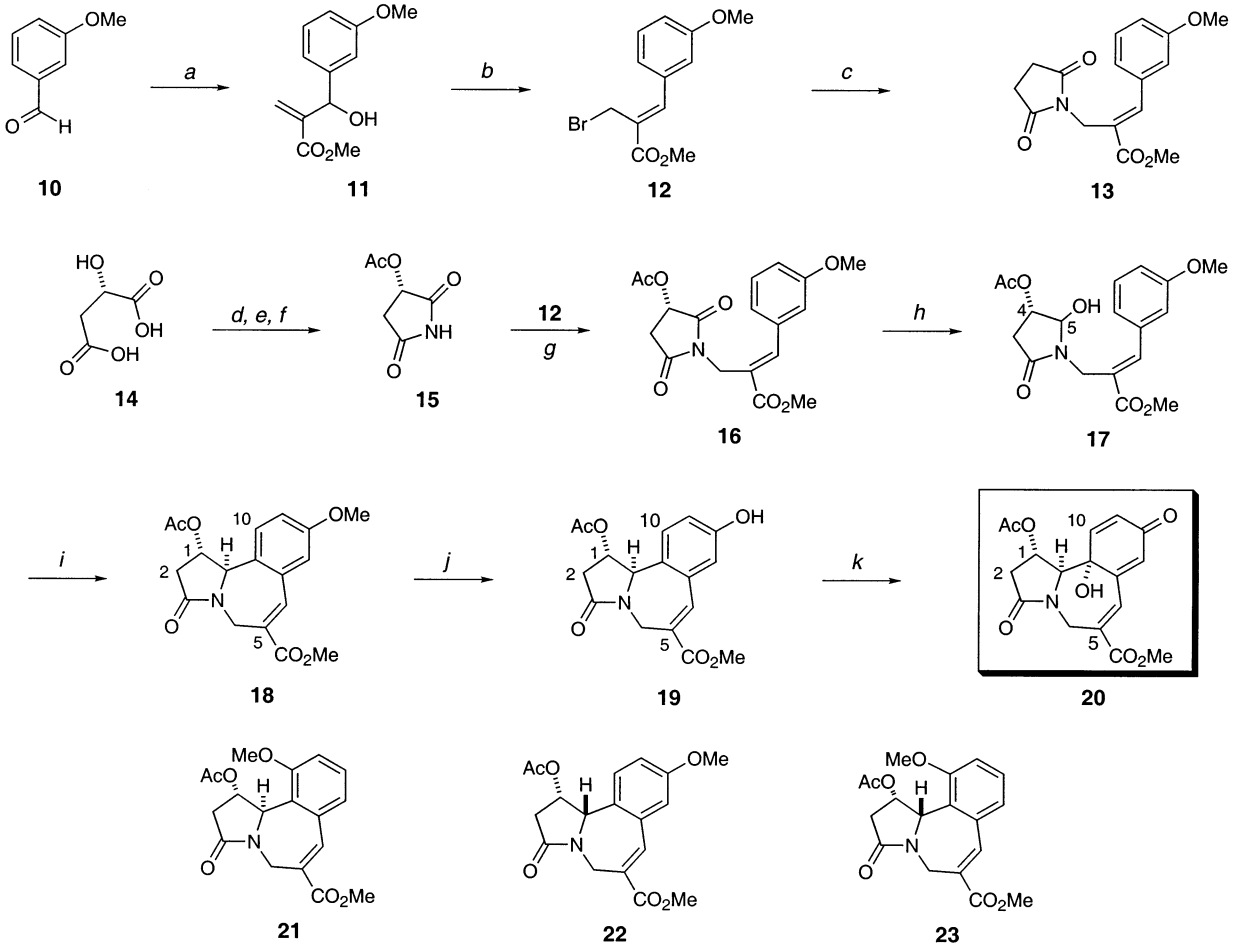
(17) (a) Chamberlain, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (b) Almeida, J. F.; Anaya, J.; Martin, N.; Grande, M.; Moran, J. R.; Caballero, C. *Tetrahedron: Asymmetry* **1992**, *3*, 1431.

(18) For a review on trifluoromethanesulfonic acid see: Stang, P. J.; White, M. R. *Aldrichimica Acta* **1983**, *16*, 15.

(19) A 3:1 para/ortho-isomeric ratio has been demonstrated for cyclizations that afford aromatic steroid precursors: Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.

(20) (a) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435. (b) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927.

**SCHEME 2. Synthesis of an Enantiopure Azaditerpenoid Analogue**[a]




[a] (a) Methyl acrylate, 3-hydroxyquinuclidine (91%); (b) 48% HBr (aq), 16 h, 20 °C (80%); (d) AcCl; (e) ammonia; (f) AcCl; 50% overall for (d)−(f); (g) $K_2CO_3$, DMF (62%); (h) $NaBH_4$, MeOH, HCl (87%); (i) 5% $CF_3SO_3H$ in dichloromethane, 75 min, 20 °C (65%); (j) $BBr_3$ (70%); (k) PIFA (12%).

*sponding to the 9a-hydroxy group and the 10a-hydrogen atom in phorbol, gnidicin, gnidimacrin, and resiniferatoxin, among other related diterpenoids. Additionally, the absolute configurations of* **18** *and* **20** *are analogous to those in phorbol and related diterpenoids, and follow from the (3S)-configuration of imide* **15**.

In dienone **20**,[21] the O(1)−H(1) and H(1)−O(4) distances of 0.82 and 1.895 Å are consistent with intermolecular hydrogen bonding to solvent incorporated into the crystal structure (refining as $C_{17}H_{17}NO_7 \cdot 0.5(^iPrOH)$) This is a significant finding, since the corresponding O-atoms at C-4 and C-9 in phorbol interact with receptor sites, and hydrogen bonding in phorbol[2,22] and its solvates[23] usually involves both of those oxygen atoms, though *independently of each other*. Additionally, the methoxycarbonyl group in **20** lies out of the plane defined by C(5)−C(6)−C(7); in the same way, the degree of noncoplanarity of the C-20 side chain with the C=C unsaturation in the seven-membered ring of phorbol derivatives can moderate the pharmacological properties. *The dienone* **20** *incorporates oxygenated functionality corresponding to the C-9 and C-20 positions in phorbol, which together with C-4 is crucial to biological activity.*[3] *The ability of both O(1) and O(4) to engage in hydrogen bonding supports the possibility of* **20** *and related systems being pharmacologically significant through binding to receptor sites.* As expected, during cyclization of the precursor **17**, the α-face attachment of the 1-acetoxy group induced approach of the aromatic ring to the opposite, less hindered, *β*-face, resulting in a 10bα-configuration of the tricyclic systems.[17]

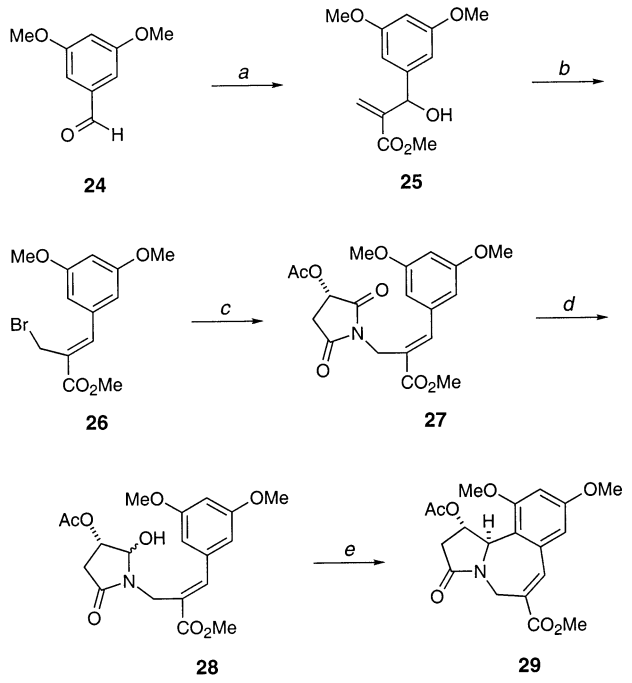
Other cyclizations were also successful (Scheme 3). Structural modifications were sought which would improve the selectivity of the cyclization step. It was anticipated that the introduction of a second methoxy group to the aromatic ring would increase steric inter-

(21) Crystal data for **20**: $(C_{17}H_{17}NO_7)\cdot 0.5(C_3H_8O)$, $M_r$ = 377.36, orthorhombic, $C222_1$ (No. 20), $a$ = 20.254(5) Å, $b$ = 23.722(8) Å, $c$ = 7.913(3) Å, $U$ = 3802(2) Å$^3$, $Z$ = 8, $D_c$ = 1.319 g cm$^{-3}$, $\mu$(Mo Kα) = 1.03 cm$^{-1}$, $F(000)$ = 1592, $T$ = 293(2) K. Crystallographic measurements were made using a FAST area detector diffractometer and Mo Kα radiation ($\lambda$ = 0.71069 Å). The structure was solved by direct methods (SHELX-S) and refined on $F^2$ by full-matrix least-squares (SHELXL-93) using all 2890 unique data to final $R_w$ (on $F^2$) = 0.1166 and $R$ (on $F$) = 0.0565 (for data with $F_o > 4\sigma F_o$)), non-H atoms anisotropic; H atoms on the solvent ignored, others in riding model with $U_{iso}$ tied to the $U_{eq}$ of the parent. Cambridge Crystallographic Data Base Deposition Number CCDC 191807.

(22) Pettersen, R. C.; Birnbaum, G. I.; Ferguson, G.; Islam, K. M. S.; Sime, J. G. *J. Chem. Soc. B* **1968**, 980.

(23) Hoppe, W.; Zechmeister, K.; Röhrl, M.; Brandl, F.; Hecker, E.; Kreibich, G.; Bartsch, H. *Tetrahedron Lett.* **1969**, 667.

**SCHEME 3**[a]



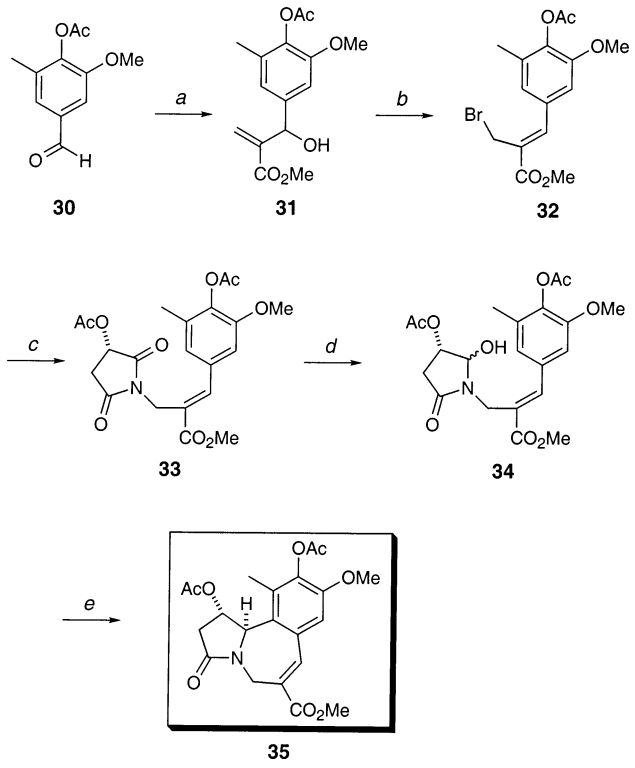

[a] (a) Methyl acrylate, 3-hydroxyquinuclidine (0.2 equiv), $CH_2Cl_2$ (80%); (b) 48% HBr (aq) (87%); (c) **15**, $K_2CO_3$, DMF (70%); (d) $NaBH_4$, MeOH, −8 °C, 20 min, quantitative; (e) 5% $CF_3SO_3H$ in $CH_2Cl_2$ (80%).

actions arising from α-face attack on cyclization in addition to avoiding regioisomeric products, since the hydroxylactam **28** is symmetrical to ortho- and para-attack. The strategy of Scheme 3 employed 3,5-dimethoxybenzaldehyde (**24**) in a Baylis−Hillman reaction with methyl acrylate (3-hydroxyquinuclidine, $CH_2Cl_2$, 80%). In this case, it was found necessary to increase the proportion of catalyst used to 0.2 equiv for an efficient reaction to occur. Bromide **26** was then formed by treatment of the alcohol **25** with aqueous 48% hydrobromic acid (87%). N-Alkylation of (3*S*)-acetoxysuccinimide **15** ($K_2CO_3$, DMF, 70%) afforded the dimethoxy derivative **27**, which was reduced ($NaBH_4$, MeOH, − 8 °C, quantitative), and the epimeric mixture of **28** (6:1 cis:trans) was cyclized with 5% $CF_3SO_3H$ in dichloromethane to give the tricyclic lactam **29**, in 80% yield, as the only isomer isolated and of potential use in the synthesis of aza-aconite alkaloids.

Following the synthesis of **29**, the introduction of further functionality was attempted that more closely resembled the tumor-promoting diterpenes (Scheme 4). 5-Methylvanillin[24] was selected as a suitable precursor, since it possesses both a methyl group, which would provide a 10-substituent in the cyclized product analogous to the 11-methyl group of the natural systems, and a 4-hydroxyl function that would enable the introduction of long chain esters analogous to the esters at position-12 of the gnididin types. Such aliphatic esters are crucial to the biological activity of the natural systems and improve penetration of lipids. To facilitate the Baylis−Hillman reaction with methyl acrylate (Scheme 4), 5-methylvanillin was converted into the acetate **30**. In a

(24) Sinhababu, A. K.; Borcharst, R. T. *Synth. Commun.* **1983**, *13*, 677.

**SCHEME 4**[a]




[a] (a) Methyl acrylate, 3-hydroxyquinuclidine (0.2 equiv), $CH_2Cl_2$ (51%); (b) 48% HBr (aq), quantitative; (c) **15**, $K_2CO_3$, DMF (73%); (d) $NaBH_4$, MeOH, −8 °C, 20 min (87%); (e) 5% $CF_3SO_3H$ in $CH_2Cl_2$.

sequence analogous to Scheme 3, alcohol **31** was converted into the tetrasubstituted benzenoid precursor **33,** which was reduced ($NaBH_4$, MeOH, −8 °C, 87%), and the 4:1 epimeric mixture of the hydroxy lactam was cyclized with 5% $CF_3SO_3H$ in dichloromethane to give lactam **35** in 60% yield. The regiochemistry of the lactam **35** was established by rotating-frame Overhauser enhancement NMR spectroscopy. The observed interaction between the methoxy hydrogen atoms at position-8 and the hydrogen atom at position-7 indicated their proximity; no such interaction was observed for the 10-methyl group and hydrogen atom at position-7. Accordingly, ring closure is inferred to have taken place para to the methoxy group, as desired. The dense C-ring substitution of **35** is suitable for development into analogues of gnididin and phorbol.

Although cyclizations involving acyliminium species that afford six-membered rings[11] are abundant, the present examples supplement the few acyliminium cyclizations that result in a seven-membered ring.[25] The succinct enantioselective syntheses of the tricyclic lactams **18**, **29**, and **35**, and of the tricyclic carbinol **20** establish a convergent strategy for the synthesis of highly functionalized aza analogues of natural products that incorporate an angularly fused 5−7−6 tricyclic system. Suitable modifications of such lactams can be envisaged, including (a) elimination of acetic acid across the 1,2-positions, (b) electrophilic substitution and/or oxidation

(25) (a) Moeller, K. D.; Rothfus, S. L.; Wong, P. L. *Tetrahedron* **1991**, *47*, 583. (b) Liao, Z.-K.; Kohn, H. *J. Org. Chem.* **1984**, *49*, 4745. (c) Massa, S.; Mai, A.; Artico, M.; Corelli, F.; Botta, M. *Tetrahedron* **1989**, *45*, 2763. (d) Kraus, G. A., Yue, S. *J. Org. Chem.* **1983**, *48*, 2936.

of the aromatic ring, and (c) manipulation of the C-5 ester group to give the desired pharmacological activity.[3]

## Experimental Section

**General.** Melting points were determined on a microscope hot stage and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded at 250 and 68.8 MHz, respectively, in $CDCl_3$ unless otherwise stated. Thin-layer chromatography was performed on 0.2 mm aluminum-backed silica plates and visualized using ultra violet light or developed using an alkaline potassium permanganate spray. Flash column chromatography was performed using silica gel. Petroleum ether (40−60 °C fraction) and ethyl acetate were distilled prior to use, dichloromethane was distilled over calcium hydride, and THF was distilled from sodium and benzophenone. Evaporation refers to the removal of solvent under reduced pressure.

5-Methylvanillin[24] and (3*S*)-acetoxysuccinimide[17a] were prepared according to literature procedures.

**Methyl 3-(3-Methoxyphenyl)-2-(bromomethyl)propenoate (12).**[13] A mixture of **9** (4.00 g, 29.4 mmol) and methyl propenoate (3.16 g, 36.7 mmol) was treated with a solution of 3-hydroxyquinuclidine (0.19 g, 1.47 mmol) in dichloromethane (1 mL). The mixture was stirred at 20 °C for 3 days before the volatile components were evaporated. The viscous oil was treated with aqueous hydrobromic acid (30 mL, 48%), and the mixture was stirred at 20 °C for 16 h and then poured into diethyl ether (75 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 100 mL), dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (1:10 ethyl acetate/light petroleum) to give **12** (6.62 g, 79%) as a colorless oil: $\nu_{max}$ (film) 2900, 2795, 1710, 1610, 1590 cm$^{-1}$; $\delta_H$ 7.82 (1H, s), 7.37 (1H, t, $J$ = 8.0 Hz), 7.13 (2H, m), 6.97 (1H, m), 4.40 (2H, s), 3.90 (3H, s), 3.85 (3H, s); $\delta_C$ 166.6 (s), 159.8 (s), 143.0 (d), 135.5 (s), 129.9 (d), 128.8 (s), 122.9 (d), 115.9 (d), 114.2 (d), 55.4 (q), 52.5 (q), 27.0 (t); *m*/*z* (EI) 286 (7), 284 (7), 205 (60), 145 (100), 131 (15), 115 (31), 103 (25). HRMS Calcd for $C_{12}H_{13}{}^{79}BrO_3$: 284.0048. Found: 284.0045.

**1-[2-Carbomethoxy-3-(3-methoxyphenyl)-2-propenyl)]-pyrrolidine-2,5-dione (13).** The bromide **12** (1.00 g, 3.34 mmol) was added to a solution of succinimide (0.33 g, 3.34 mmol) in DMF (1 mL), and the mixture was washed in with more solvent (1 mL). Anhydrous potassium carbonate (0.46 g, 3.34 mmol) was added in small portions (to minimize ring opening), and the mixture was stirred at 20 °C for 16 h. Dichloromethane (20 mL) was then added, and the solution was poured into water (80 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with water (2 × 25 mL), dried over magnesium sulfate, and filtered, and the solvent was evaporated. Purification by column chromatography (1:1 ethyl acetate/light petroleum) gave **13** (0.81 g, 80%) as a viscous, colorless oil: $\nu_{max}$ (film) 1777, 1705 cm$^{-1}$; $\delta_H$ 7.86 (1H, s), 7.29 (1H, t, $J$ = 7.0 Hz), 6.80 (3H, m), 4.57 (2H, s), 3.82 (3H, s), 3.79 (3H, s), 2.51 (4H, s); $\delta_C$ 176.7 (s), 176.6 (s), 166.7 (s), 159.5 (s), 142.6 (d), 135.9 (s), 129.6 (d), 125.9 (s), 121.0 (d), 114.6 (d), 113.8 (d), 52.3 (q), 52.2 (q), 36.6 (t), 28.0 (t), 28.0 (t).

**[1-[2-Carbomethoxy-3-(3-methoxyphenyl)-2-propenyl)]-(3*S*)-acetoxy-pyrrolidine-2,5-dione (16).** (3*S*)-Acetoxysuccinimide (**15**) (2.20 g, 14.0 mmol) was dissolved in DMF (5 mL). To this solution was added bromide **12** (3.99 g, 14.0 mmol), and the residues were washed in with more solvent (1 mL). Anhydrous potassium carbonate (1.94 g, 14.0 mmol) was added in small portions, and the mixture was stirred under nitrogen for 2.5 h. Dichloromethane (80 mL) was added, and the solution was poured into water (300 mL). The aqueous layer was separated and extracted with dichloromethane (3 × 150 mL). The combined organic layers were dried over sodium sulfate and filtered, and the solvent was evaporated to give a solid that was purified by column chromatography (1:1 ethyl acetate/light petroleum) to afford **16** as a viscous colorless oil (3.16 g, 62%): $\nu_{max}$ (film) 1749, 1720 cm$^{-1}$; $\delta_H$ 7.88 (1H, s), 7.25 (1H, t, $J$ = 5.0 Hz), 6.86 (3H, m), 5.15 (1H, dd, $J$ = 9, 5.5 Hz), 4.56 (2H, s), 3.76 (3H, s), 3.73 (3H, s), 2.92 (1H, dd, $J$ = 18.0, 9.0 Hz), 2.43 (1H, dd, $J$ = 18.0, 5.5 Hz), 2.07 (3H, s); $\delta_C$ 172.9 (s), 172.5 (s), 169.7 (s), 166.6 (s), 159.6 (s), 143.2 (d), 135.8 (s), 129.7 (d), 125.3 (s), 121.0 (d), 114.8 (d), 113.9 (d), 67.1 (d), 55.3 (q), 52.2 (q), 36.8 (t), 35.6 (t), 20.5 (q); *m*/*z* (EI) 361 (100%), 329 (47), 269 (31), 241 (83), 204 (49), 172 (71), 145 (50), 69 (47), 55 (60). HRMS Calcd for $C_{18}H_{19}NO_7$: 361.1162. Found: 361.1166.

**1-[2-Carbomethoxy-3-(3-methoxyphenyl)-2-propenyl]-(4*S*)-acetoxy-5-hydroxy-pyrrolidin-2-one (17).** The imide **16** (0.50 g, 1.38 mmol) was stirred in methanol (45 mL) at −8 °C. To this was added sodium borohydride (0.26 g, 6.92 mmol) and stirring was continued for 20 min, before pouring into a stirred mixture of saturated aqueous sodium hydrogen carbonate solution (40 mL) and dichloromethane (40 mL). The aqueous layer was extracted with additional dichloromethane (3 × 30 mL). The combined organic layers were dried over magnesium sulfate and filtered, and the solvent was evaporated to give the product as a mixture of diastereoisomers (2.5:1 cis/trans, 0.44 g, 87%) which was then recrystallized from dichloromethane−light petroleum to afford amide **17** (0.25 g, 50%) as white prisms of a single diastereoisomer, mp 111−113 °C: $\nu_{max}$ (Nujol mull) 3165, 1733, 1708, 1664 cm$^{-1}$; $\delta_H$ 7.92 (1H, s), 7.58 (1H, t, $J$ = 5.0 Hz), 7.02 (2H, m), 6.94 (1H, m), 5.25 (1H, d, $J$ = 6.0 Hz), 5.05 (1H, m), 4.75 (1H, d, $J$ = 8.0 Hz), 4.19 (1H, d, $J$ = 8.0 Hz), 3.88 (3H, s), 3.57 (3H, s), 2.67 (2H, d, $J$ = 7.5 Hz), 2.15 (3H, s); $\delta_C$ 171.0 (s), 170.6 (s), 169.3 (s), 159.7 (s), 145.1 (d), 135.2 (s), 129.8 (d), 125.6 (s), 122.3 (d), 115.9 (d), 114.5 (d), 80.7 (d), 67.6 (d), 55.4 (q), 52.7 (q), 37.3 (t), 34.3 (t), 20.7 (q). Anal. Calcd for $C_{18}H_{22}NO_7$: C, 59.33; H, 5.99; N, 3.84. Found: C, 59.48; H, 5.82; N, 3.81.

**1α-Acetoxy-5-carbomethoxy-1,2,4,10bα-tetrahydro-8-methoxy-3a-azabenz[*e*]azulen-3-one (18).** The lactam **17** (0.20 g, 0.55 mmol; 2.5:1 cis/trans) was dissolved in dichloromethane (0.95 mL) under nitrogen. Trifluoromethanesulfonic acid (0.05 mL) was added, and the mixture was stirred for 1.5 h. Saturated aqueous sodium hydrogen carbonate was added cautiously to neutralize the excess acid. The mixture was diluted with water (15 mL), and the product was extracted with dichloromethane (3 × 20 mL). The combined extracts were dried over magnesium sulfate, filtered, and evaporated to give a mixture of **18** and **21** (70% yield determined by $^1$H NMR spectroscopy). Two recrystallizations from ethyl acetate−light petroleum afforded the single diastereoisomer **18** (35 mg, 18%) as microprisms, mp 180−182 °C: $\alpha_D{}^{20}$ +144° (*c* = 0.1, $CHCl_3$); $\nu_{max}$ (Nujol mull) 1736, 1717, 1692 cm$^{-1}$; $\delta_H$ 7.56 (1H, s), 7.47 (1H, d, $J$ = 8.0 Hz), 6.86 (2H, m), 5.53 (1H, m), 4.79 (1H, d, $J$ = 2.0 Hz), 4.67 (1H, d, $J$ = 18.0 Hz), 4.06 (1H, d, $J$ = 18.0 Hz), 3.79 (3H, s), 3.77 (3H, s), 2.74 (1H, dd, $J$ = 18.0, 6.0 Hz), 2.39 (1H, dd, $J$ = 18.0, 2.0 Hz), 2.18 (3H, s); $\delta_C$ 171.9 (s), 170.6 (s), 166.4 (s), 159.1 (s), 140.7 (d), 134.4 (s), 130.5 (s), 129.7 (s), 128.0 (d), 119.2 (d), 115.4 (d), 111.7 (d), 72.9 (d), 66.9 (d), 55.4 (q), 52.4 (q), 40.8 (t), 36.3 (t), 21.1 (q). Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.57; H, 5.60; N, 4.22.

**1α-Acetoxy-5-carbomethoxy-1,2,4,10bα-tetrahydro-8-hydroxy-3a-azabenz[*e*]azulen-3-one (19).** The lactam **18** (100 mg, 0.29 mmol) was stirred in dichloromethane (1 mL) under nitrogen. Boron tribromide in dichloromethane (2.0 mL, 1 M) was added, and stirring was continued for 1.5 h. The mixture was then poured into water (10 mL) and extracted with dichloromethane (4 × 10 mL). The combined organic extracts were then dried over sodium sulfate and filtered, and the solvent was evaporated. The residue was purified by column chromatography (8:2 ethyl acetate/light petroleum) to afford **19** (67 mg, 70%) as an oil: $\delta_H$ 7.54 (1H, s), 7.45 (1H, d, $J$ = 8.0 Hz), 6.86 (2H, m), 5.56 (1H, m), 4.83 (1H, d, $J$ = 2.0

Hz), 4.72 (1H, d, $J$ = 18.0 Hz), 4.11 (1H, d, $J$ = 18.0 Hz), 3.78 (3H, s), 2.77 (1H, dd, $J$ = 18.0, 6.0 Hz), 2.45 (1H, dd, $J$ = 18.0, 2.0 Hz), 2.13 (3H, s); $\delta_C$ 171.4 (s), 170.8 (s), 166.6 (s), 156.6 (s), 141.3 (d), 134.2 (s), 129.7 (s), 128.3 (s), 128.1 (d), 121.0 (s), 117.2 (s), 72.9 (d), 67.3 (d), 52.5 (q), 40.9 (t), 36.5 (t), 21.1 (q); *m*/*z* EI 331 (0.5%), 314 (6), 271 (39), 256 (11), 173 (17). HRMS Calcd for $C_{17}H_{17}NO_6$: 331.1056. Found: 331.1058.

**1α-Acetoxy-5-carbomethoxy-10aα-hydroxy-8-oxo-1,2,-10aα,10bα-tetrahydro-4*H*-3a-azabenz[*e*]azulene-3,8-dione (20).** The phenol **19** (293 mg, 0.88 mmol) was stirred at 0 °C in acetonitrile/water (12 mL, 4:1). Bis(trifluoroacetoxy)-iodobenzene (PIFA, 456 mg, 1.06 mmol) was added, and stirring was continued for 50 min. Solid sodium hydrogen carbonate was added to neutralize the mixture, which was then evaporated. The residue was diluted with water (10 mL) and extracted with dichloromethane (4 × 15 mL). The combined organic extracts were dried over sodium sulfate and filtered, and the solvent was evaporated. The residue was purified by column chromatography (8:2 ethyl acetate/light petroleum) to afford **20** (38 mg, 12%) as white microprisms, mp 128−130 °C: $\alpha_D^{20}$ +307° ($c$ = 0.043, $CHCl_3$); $\delta_H$ 7.43 (1H, bd s), 7.04 (1H, d, $J$ = 8.5 Hz), 6.78 (1H, dd, $J$ = 8.5, 3.0 Hz), 6.64 (1H, d, $J$ = 3.0 Hz), 5.38 (1H, dd, $J$ = 6.5, 1.5 Hz), 5.37 (1H, s), 4.97 (1H, dd, $J$ = 18.5, 1.5 Hz), 4.00 (1H, dd, $J$ = 18.5, 2.0 Hz), 3.84 (3H, s), 2.12 (3H, s), 2.09 (1H, d, $J$ = 8.5 Hz), 2.13−2.05 (2H, m); *m*/*z* (EI) 347 (91%), 305 (38), 279 (29), 255 (58), 205 (60), 191 (77), 147 (100). HRMS Calcd for $C_{17}H_{17}NO_7$: 347.1005. Found: 347.1002.

**Methyl 2-[(3,5-Dimethoxyphenyl)hydroxymethyl]-propenoate (25).** 3,5-Dimethoxybenzaldehyde (3.32 g, 20.0 mmol) and methyl acrylate (8.61 g, 100 mmol) were stirred together under nitrogen until the mixture was homogeneous. 3-Hydroxyquinuclidine (0.51 g, 4.00 mmol) in dichloromethane (2 mL) was added, and the mixture was stirred 20 °C for 4 days. The excess methyl acrylate was then removed in vacuo, and the residue was purified by column chromatography (3:7 ethyl acetate/light petroleum) to give **25** (4.33 g, 86%) as a colorless oil: $\nu_{max}$ (film) 3484, 1715 $cm^{-1}$; $\delta_H$ 6.5 (2H, d, $J$ = 3.0 Hz), 6.35 (1H, t, $J$ = 2.0 Hz), 6.3 (1H, s), 5.8 (2H, t, $J$ = 2.0 Hz), 3.75 (6H, s), 3.7 (3H, s); $\delta_C$ 166.8 (s), 160.8 (s), 143.9 (s), 141.7 (s), 126.2 (t), 104.6 (d), 99.7 (d), 73.0 (d), 55.3 (q), 51.9 (q). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.55; H, 6.06.

**Methyl 2-(Bromomethyl)-3-(3,5-dimethoxyphenyl)propenoate (26).** The alcohol **25** (3.70 g, 14.6 mmol) was stirred overnight with aqueous hydrobromic acid (40 mL, 48%). Following neutralization (1 M sodium hydroxide) the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with water (2 × 40 mL), dried over magnesium sulfate, and filtered, and the solvent was evaporated. The crude residue was purified by column chromatography (3:7 ethyl acetate/light petroleum) to give **26** as white microprisms (4.02 g, 87%), mp 50−55 °C: $\nu_{max}$ (Nujol mull) 1712 $cm^{-1}$; $\delta_H$ 7.75 (2H, s), 6.75 (2H, d, $J$ = 2.0 Hz), 6.50 (1H, t, $J$ = 2.0 Hz), 4.40 (2H, s), 3.90 (3H, s), 3.80 (6H, s); $\delta_C$ 166.5 (s), 161.0 (s), 161.0 (s), 143.2 (d), 136.0 (s), 129.0 (s), 107.2 (d), 107.2 (d), 102.2 (d), 55.5 (q), 55.5 (q), 52.5 (q), 21.0 (t). Anal. Calcd for $C_{13}H_{15}BrO_4$: C, 49.54; H, 4.79; Br, 25.35. Found: C, 49.76; H, 4.83; Br, 25.31.

**1-[2-Carbomethoxy-3-(3,5-dimethoxyphenyl)-2-propenyl]-(3*S*)-acetoxy-pyrrolidine-2,5-dione (27).** (3*S*)-Acetoxysuccinimide (**15**)[17a] (1.89 g, 12.0 mmol) was dissolved in DMF (5 mL) and stirred with the bromide **26** (3.80 g, 12.1 mmol). Anhydrous potassium carbonate (1.66 g, 12.0 mmol) was then added in small portions, and the mixture was stirred under nitrogen for 2.5 h. Dichloromethane (80 mL) was added, and the solution was poured into water (200 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over magnesium sulfate and filtered, and the solvent was evaporated. Column chromatography (2:3 ethyl acetate/light petroleum) afforded **27** (3.30 g, 70%) as a viscous, colorless oil: $\nu_{max}$ (Nujol mull) 1750, 1720, 1715 $cm^{-1}$; $\delta_H$ 7.83 (1H, s), 6.50 (2H, d, $J$ = 2.0 Hz), 6.40 (1H, t, $J$ = 2.0 Hz), 5.20 (1H, dd, $J$ = 9.5, 5.5 Hz), 4.60 (2H, s), 3.75 (9H, s), 2.95 (1H, dd, $J$ = 18.0, 9.5 Hz), 2.50 (1H, dd, $J$ = 18.0, 5.5 Hz), 2.10 (3H, s); $\delta_C$ 172.9 (s), 172.6 (s), 169.7 (s), 166.5 (s), 160.8 (s), 143.1 (d), 136.3 (s), 125.6 (s), 106.4 (d), 101.0 (d), 67.1 (d), 55.4 (q), 52.2 (q), 36.7 (t), 35.5 (t), 20.4 (q). Anal. Calcd for $C_{19}H_{21}NO_8$: C, 58.31; H, 5.41; N, 3.57. Found: C, 59.68; H, 5.49; N, 3.33.

**1-[2-Carbomethoxy-3-(3,5-dimethoxyphenyl)-2-propenyl]-(4*S*)-acetoxy-5-hydroxypyrrolidin-2-one (28).** The imide **27** (2.64 g, 6.74 mmol) was stirred in methanol (250 mL) at −8 °C. Sodium borohydride (1.30 g, 34.5 mmol) was added, and after being stirred for 20 min the mixture was poured into a stirred mixture of saturated aqueous sodium hydrogen carbonate (150 mL) and dichloromethane (150 mL). The organic layer was separated, and the aqueous layer was further extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over magnesium sulfate and filtered, and the solvent was evaporated to give the product as a mixture of diastereoisomers (6:1 cis/trans, quantitative) which was recrystallized from ethyl acetate−light petroleum to give the pure cis amide **28** (1.83 g, 69%) as white prisms, mp 100−103 °C: $\nu_{max}$ (Nujol mull) 3225, 1734, 1709, 1694 $cm^{-1}$; $\delta_H$ 7.80 (1H, s), 6.55 (2H, d, $J$ = 2.0 Hz), 6.42 (1H, t, $J$ = 2.0 Hz), 5.19 (1H, d, $J$ = 5.5 Hz), 5.00 (1H, m), 4.67 (1H, d, $J$ = 15.5 Hz), 4.08 (1H, d, $J$ = 15.5 Hz), 3.79 (3H, s), 3.73 (6H, s), 2.60 (2H, d, $J$ = 9.5 Hz), 2.07 (3H, s); $\delta_C$ 171.0 (s), 170.6 (s), 169.2 (s), 160.9 (s), 145.2 (d), 135.7 (s), 125.8 (s), 107.5 (d), 102.3 (d), 80.7 (d), 67.6 (d), 55.5 (q), 52.7 (q), 37.3 (t), 34.3 (t), 20.7 (q). Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.02; H, 5.89; N, 3.56. Found: C, 58.04; H, 5.57; N, 3.60.

**1α-Acetoxy-5-carbomethoxy-1,2,4,10bα-tetrahydro-8,-10-dimethoxy-3a-azabenz[*e*]azulen-3-one (29).** Trifluoromethanesulfonic acid (0.05 mL) was added to a stirred solution of **28** (0.20 g, 0.51 mmol) in dichloromethane (1 mL) under nitrogen, and stirring was continued for 2 h. Saturated aqueous sodium hydrogen carbonate was then added cautiously until the solution was neutral. The mixture was diluted with water (15 mL) and extracted with dichloromethane (3 × 20 mL). The combined extracts were washed with water (20 mL) and then with brine (20 mL), dried over magnesium sulfate, and filtered, and the solvent was evaporated. Purification by column chromatography (1:1 ethyl acetate/light petroleum) gave **29** (0.13 g, 80%) as white microprisms, mp 185−187 °C: $\alpha_D^{20}$ −269° ($c$ = 0.1, $CHCl_3$); $\nu_{max}$ (Nujol mull) 1727, 1709, 1694 $cm^{-1}$; $\delta_H$ 7.35 (1H, d, $J$ = 2.0 Hz), 6.45 (1H, d, $J$ = 2.0 Hz), 6.40 (1H, d, $J$ = 2.0 Hz), 5.25 (1H, d, $J$ = 6.3 Hz), 5.10 (1H, m), 4.90 (1H, d, $J$ = 18.0 Hz), 3.75 (9H, s), 3.55 (1H, dd, $J$ = 18.0, 2.0 Hz), 2.60 (1H, dd, $J$ = 18.0, 9.0 Hz), 2.20 (1H, d, $J$ = 18.0 Hz), 2.10 (3H, s); $\delta_C$ 171.9 (s), 169.8 (s), 166.4 (s), 159.9 (s), 158.7 (s), 140.6 (d), 134.2 (s), 133.1 (s), 120.7 (s), 110.6 (d), 100.0 (d), 73.0 (d), 67.4 (d), 55.8 (q), 55.0 (q), 52.3 (q), 39.8 (t), 37.3 (t), 21.1 (q). Anal. Calcd for $C_{19}H_{21}NO_7$: C, 60.85; H, 5.64; N, 3.76. Found: C, 60.64; H, 5.45; N, 3.65.

**4-Acetoxy-3-methoxy-5-methylbenzaldehyde (30).** A solution of acetyl chloride (30.6 mL, 0.34 mol) in dichloromethane (420 mL) was added dropwise to a well-stirred mixture of 5-methylvanillin[24] (60.0 g, 0.36 mol), dichloromethane (1.5 L), tetrabutylammonium hydrogen sulfate (480 mg), and powdered sodium hydroxide (36.1 g, 0.90 mol) over 90 min. The mixture was stirred at 20 °C for 3 h and then diluted with water (1.0 L), and the product was extracted with dichloromethane (3 × 800 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and evaporated. Column chromatography (4:1 ethyl acetate/light petroleum) afforded **30** (48.8 g, 65%) as white prisms, mp 58 °C: $\nu_{max}$ (Nujol mull) 1764, 1691 $cm^{-1}$; $\delta_H$ 9.40 (1H, s), 7.35 (1H, s), 7.32 (1H, s), 3.86 (3H, s), 2.36 (3H, s), 2.24 (3H, s); *m*/*z* (EI) 208 (12%), 166 (100%), 165 (49%). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.45; H, 5.84.

**Methyl 2-[(4-Acetoxy-3-methoxy-5-methylphenyl)hydroxymethyl]propenoate (31).** The aldehyde **30** (14.0 g, 67.2 mmol) was stirred under nitrogen with methyl acrylate (7.24 g, 84.0 mol) in dichloromethane (5 mL). 3-Hydroxyquinuclidine (1.71 g, 13.4 mmol) in dichloromethane (5 mL) was added, and the solution was stirred at 20 °C for 4 days. The mixture was concentrated in vacuo to remove the solvent and excess methyl acrylate. The oily residue was subjected to column chromatography (light petroleum/ethyl acetate (4:1 increased to 7:3)) to give alcohol **31** (10.1 g, 51%) as a viscous oil: $\nu_{max}$ (film) 3493 (br), 1761, 1722 cm$^{-1}$; $\delta_H$ 6.84 (1H, s), 6.77 (1H, s), 6.32 (1H, s), 5.85 (1H, s), 5.48 (1H, d, $J$ = 6.0 Hz), 3.77 (3H, s), 3.72 (3H, s), 3.13 (1H, d, $J$ = 6.0 Hz), 2.30 (3H, s), 2.13 (3H, s); $\delta_C$ 168.9 (s), 166.7 (s), 151 (s), 141.8 (s), 139.5 (s), 137.8 (s), 131.2 (s), 126.0 (t), 120.6 (d), 108.2 (d), 72.6 (d), 55.9 (q), 52.0 (q), 20.4 (q), 16.0 (q); *m*/*z* (EI) 294 (54%), 252 (100%), 220 (45%), 192 (32%), 167 (36%), 165 (72%), 138 (43%), 84 (29%). HRMS Calcd for $C_{15}H_{18}O_4$: 294.1103. Found: 294.1097.

**Methyl 3-(4-Acetoxy-3-methoxy-5-methylphenyl)-2-(bromomethyl)propenoate (32).** The alcohol **31** (7.00 g, 23.8 mmol) was stirred in aqueous hydrobromic acid (100 mL, 48%) for 16 h and then poured into diethyl ether (150 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 150 mL), dried over magnesium sulfate, filtered, and evaporated. The residue was purified by column chromatography (5:95 ethyl acetate/light petroleum) to give **32** (8.35 g, 98%) as white prisms, mp 82−83 °C: $\nu_{max}$ (Nujol mull) 1748, 1723 cm$^{-1}$; $\delta_H$ 7.76 (1H, s), 7.15 (1H, d, $J$ = 1.0 Hz), 7.01 (1H, d, $J$ = 1.0 Hz), 4.42 (2H, s), 3.87 (3H, s), 3.86 (3H, s), 2.36 (3H, s), 2.21 (3H, s); $\delta_C$ 168.4 (s), 166.4 (s), 151.2 (s), 142.7 (d), 139.3 (s), 132.2 (s), 132.0 (s), 128.3 (s), 124.5 (d), 110.6 (d), 56.0 (q), 52.4 (q), 27.1 (t), 20.3 (q), 16.0 (q). Anal. Calcd for $C_{15}H_{17}BrO_5$: C, 50.44; H, 4.80; Br, 22.37. Found: C, 50.53; H, 4.94; Br, 22.34.

**1-[2-Carbomethoxy-3-(4-acetoxy-3-methoxy-5-methylphenyl)-2-propenyl]-(3*S*)-acetoxypyrrolidine-2,5-dione (33).** (3*S*)-Acetoxysuccinimide (**15**)[17a] (6.12 g, 39.0 mmol) was stirred in DMF (5 mL) at 20 °C, and to the mixture was added **32** (13.91 g, 39.0 mmol). Anhydrous potassium carbonate (5.38 g, 39.0 mmol) was then added in small portions, and the mixture was stirred under nitrogen for 3.5 h before pouring into water (800 mL). The aqueous layer was extracted with dichloromethane (4 × 300 mL), the combined organic layers were dried over sodium sulfate and filtered, and the solvent was evaporated. The oil was purified by column chromatography (3:2 light petroleum/ethyl acetate) to give the imide **33** (12.4 g, 73%) as a colorless viscous oil: $\delta_H$ 7.82 (1H, s), 6.81 (1H, d, $J$ = 1.0 Hz), 6.74 (1H, d, $J$ = 1.0 Hz), 5.09 (1H, dd, $J$ = 8.0, 5.0 Hz), 4.64 (2H, s), 3.79 (6H, s), 2.92 (1H, dd, $J$ = 18.5, 8.0 Hz), 2.44 (1H, dd, $J$ = 18.5, 5.0 Hz), 2.33 (3H, s), 2.16 (3H, s), 2.10 (3H, s); $\delta_C$ 173.0 (s), 172.8 (s), 169.7 (s), 168.7 (s), 166.6 (s), 151.0 (s), 141.9 (d), 138.6 (s), 132.4 (s), 131.8 (s), 125.2 (s), 122.5 (d), 109.7 (d), 67.2 (d), 55.9 (q), 52.3 (q), 36.8 (t), 35.3 (t), 20.4 (q), 20.4 (q), 15.8 (q); *m*/*z* (EI) 433 (12%), 391 (100%), 331 (15%), 271 (31%), 234 (19%), 203 (15%), 121 (28%). HRMS Calcd for $C_{21}H_{23}NO_9$: 433.1373. Found: 433.1367.

**1-[2-Carbomethoxy-3-(4-acetoxy-3-methoxy-5-methylphenyl)-2-propenyl)]-(4*S*)-acetoxy-5-hydroxypyrrolidin-2-one (34).** Imide **33** (0.50 g, 1.38 mmol) was stirred in methanol (45 mL) at −8 °C. Sodium borohydride (0.26 g, 6.92 mmol) was then added, and stirring was continued for 20 min. The mixture was poured into a stirred mixture of saturated aqueous sodium hydrogen carbonate (40 mL) and dichloromethane (40 mL). The aqueous layer was extracted with additional dichloromethane (3 × 30 mL). The combined organic layers were dried over magnesium sulfate and filtered, and the solvent was evaporated to give amide **34** (0.52 g, 87%) as a 4:1 ratio of cis/trans diastereoisomers. A sample was recrystallized from dichloromethane/light petroleum to give the pure cis-diastereoisomer (0.33 g, 55%) as colorless prisms, mp 120−121 °C: $\nu_{max}$ (Nujol mull) 3205 (br), 1764, 1737, 1711, 1672 cm$^{-1}$; $\delta_H$ 7.83 (1H, s), 6.95 (2H, m), 5.19 (1H, d, $J$ = 5.0 Hz), 5.00 (1H, m), 4.79 (1H, d, $J$ = 15.0 Hz), 4.11 (1H, d, $J$ = 15.0 Hz), 3.84 (3H, s), 3.81 (3H, s), 2.63 (2H, d, $J$ = 8.0 Hz), 2.32 (3H, s), 2.16 (3H, s), 2.11 (3H, s); $\delta_C$ 171.1 (s), 170.6 (s), 169.4 (s), 168.6 (s), 151.3 (s), 144.6 (d), 132.0 (s), 131.9 (s), 125.0 (s), 125.0 (s), 124.9 (d), 110.9 (d), 80.5 (d), 67.5 (d), 56.2 (q), 52.8 (q), 37.1 (t), 34.3 (t), 20.7 (q), 20.4 (q), 15.9 (q). Anal. Calcd for $C_{21}H_{25}NO_9$: C, 57.93; H, 5.79; N, 3.22. Found: C, 57.73; H, 6.08; N, 3.11.

**1α-Acetoxy-5-carbomethoxy-1,2,4,10bα-tetrahydro-9-acetoxy-8-methoxy-10-methyl-3a-azabenz[*e*]azulen-3-one (35).** The amide **34** (3.70 g, 8.50 mmol) was dissolved in dichloromethane (14.0 mL). Trifluoromethanesulfonic acid (0.75 mL, 8.50 mmol) was then added, and the mixture was stirred at 20 °C under nitrogen for 1.25 h. The mixture was then neutralized with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane, dried over sodium sulfate, and filtered, and the solvent was evaporated. Purification by column chromatography (4:1 ethyl acetate/light petroleum) afforded the single diastereoisomer **35** (2.10 g, 60%) as prisms, mp 216 °C (dec.): $\alpha_D^{20}$ −215° ($c$ = 0.1, $CHCl_3$); $\nu_{max}$ 1750, 1704 cm$^{-1}$; $\delta_H$ 7.40 (1H, d, $J$ = 2.5 Hz), 6.78 (1H, s), 5.28 (1H, s), 5.03 (1H, dt, $J$ = 6.5, 1.5 Hz), 5.01 (1H, d, $J$ = 16.5 Hz), 3.83 (3H, s), 3.82 (3H, s), 3.56 (1H, dd, $J$ = 16.5, 2.5 Hz), 2.67 (1H, dd, $J$ = 18.0, 6.5 Hz), 2.35 (3H, s), 2.28 (1H, dd, $J$ = 18.0, 1.5 Hz), 2.15 (3H, s), 2.12 (3H, s); $\delta_C$ 171.6 (s), 169.8 (s), 168.3 (s), 166.3 (s), 150.2 (s), 140.5 (d), 140.0 (s), 133.1 (s), 131.8 (s), 131.4 (s), 131.1 (s), 116.5 (d), 74.3 (d), 68.7 (d), 56.0 (q), 52.4 (q), 39.8 (t), 37.2 (t), 21.0 (q), 20.4 (q), 13.2 (q). Anal. Calcd for $C_{21}H_{23}NO_8$: C, 60.43; H, 5.55; N, 3.36. Found: C, 60.29; H, 5.69; N, 3.26.

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**Supporting Information Available:** Atomic coordinates, bond lengths, bond angles, and an ORTEP representation of **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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