Total Synthesis of Taspine

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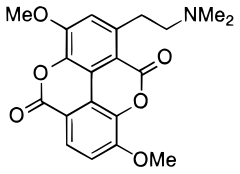
The alkaloid taspine is an active ingredient in the sap of the *Croton lechleri* tree[1] used by the Jivaro Indians of Peru to promote wound healing and to treat various maladies. Taspine (and/or its salts) also exhibits anti-inflammatory,[2] anti-ulcer,[2b] and cytotoxic activity[3] and inhibits viral DNA polymerase.[4] Extensive degradative work[5] established taspine to possess the dilactonic, tertiary amine structure **1**.

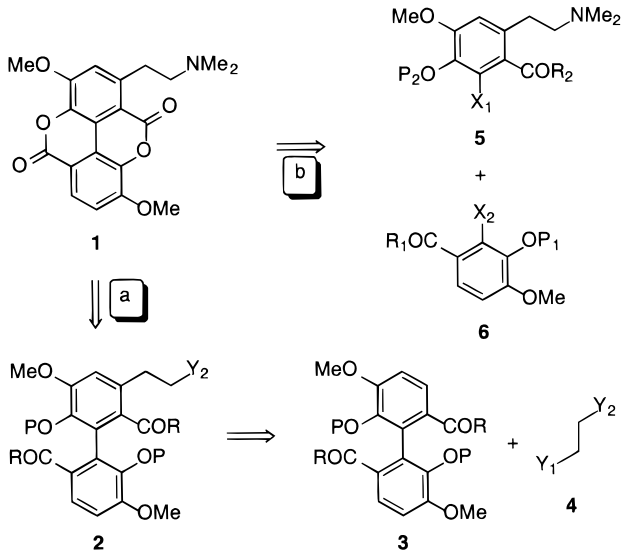


1

With no close structural relative among other nitrogen-containing natural products,[6] taspine occupies a unique position in the realm of alkaloid chemistry. Nonetheless, and despite the structural novelty and pronounced biological activity of the molecule, its total synthesis has not previously been recorded.[7,8] We now report the first total synthesis of taspine.

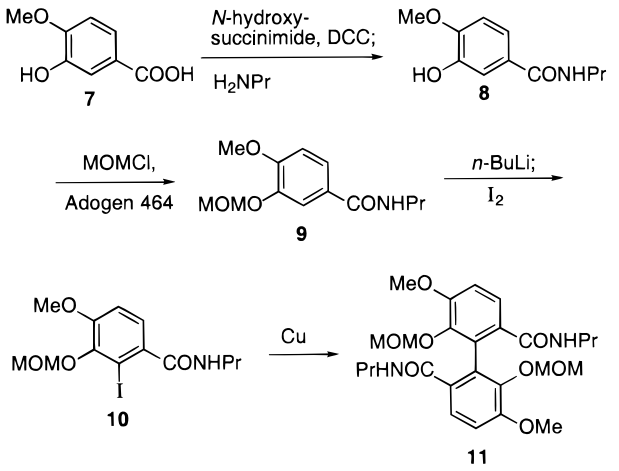
Retrosynthetic analysis suggested two possible routes for the synthesis of this natural product: routes **a** and **b** as shown in Scheme 1. We felt pathway **a** was more desirable, since our intent was to take advantage of the symmetry elements present within the taspine structure to make our synthesis convergent. Therefore, attachment of a side-chain equivalent (**4**) to the symmetrical homodimer **3** followed by bislactonization would give taspine (**1**). Homodimer **3** could originate from a monocyclic precursor (**6**) via an appropriate coupling procedure.

Scheme 1. Retrosynthetic Analysis of Taspine



X_1, X_2, Y_1, Y_2=-I,-OTf,-SnR_3,-$B(OH)_2$,etc.

Scheme 2. Synthesis of Dimer 11



Accordingly (Scheme 2), commercially available 3-hydroxy-4-methoxybenzoic acid (**7**) was converted into its *N*-propylamide (**8**) in 93% yield through a two-step, one-pot procedure.[9] Protection of the hydroxyl group as its methoxymethyl (MOM) ether[10] gave **9**. Ortho-lithiation[11]

(1) (a) Perdue, G. P.; Blomster, R. N.; Blake, D. A.; Farnsworth, N. R. *J. Pharm. Sci.* **1979**, *68*, 124−126. (b) Vaisberg, A. J.; Milla, M.; del Carmen Planas, M.; Cordova, J. L.; Rosas de Agusti, E.; Ferreyra, R.; del Carmen Mustiga, M.; Carlin, L.; Hammond, G. B. *Planta Med.* **1989**, *55*, 140−143. (c) Cai, Y.; Chen, Z. P.; Phillipson, J. D. *Phytochemistry* **1993**, *32*, 755−760. (d) Pieters, L.; De Bruyne, T.; van Poel, B.; Vingerhoets, R.; Totté, J.; Vanden Berghe, D.; Vlietinck, A. *Phytomedicine* **1995**, *2*, 17−22.

(2) (a) Persinos, G. J. (Amazon Natural Drug Co.) U.S. Patent 3 694 557, 1972; *Chem. Abstr.* **1973**, 78, 7827. (b) Lewis, W. H.; Stonard, R. J.; Porras-Reyes, B. H.; Mustoe, T. A. U.S. Patent 5 156 847, 1992; *Chem. Abstr.* **1992**, 117, 245630. (c) Porras-Reyes, B. H.; Lewis, W. H.; Roman, J.; Simchowitz, L.; Mustoe, T. A. *Proc. Soc. Exp. Biol. Med.* **1993**, *203*, 18−25. (d) Winter, R. E. K.; Kolodziej, S. A.; Lewis, W. H. U.S. Patent 5 474 782, 1995; *Chem. Abstr.* **1996**, 124, 97769.

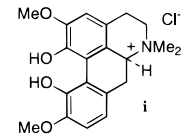
(3) (a) Itokawa, H.; Ichihara, Y.; Mochizuki, M.; Enomori, T.; Morita, H.; Shirota, O.; Inamatsu, M.; Takeya, K. *Chem. Pharm. Bull.* **1991**, *39*, 1041−1042. (b) Pieters, L.; De Bruyne, T.; Claeys, M.; Vlietinck, A.; Calomme, M.; Vanden Berghe, D. *J. Nat. Prod.* **1993**, *56*, 899−906.

(4) Sethi, M. L. *Can. J. Pharm. Sci.* **1977**, *12*, 7−9.

(5) (a) Platonova, T. F.; Kuzovkov, A. D.; Massagetov, P. S. *Zh. Obshch. Khim.* **1953**, *23*, 880−886. (b) Platonova, T. F.; Kuzovkov, A. D. *Zh. Obshch. Khim.* **1954**, *24*, 2246−2249. (c) Platonova, T. F.; Kuzovkov, A. D.; Sheinker, Yu. N. *Zh. Obshch. Khim.* **1956**, *26*, 2651−2656.

(6) (a) Shamma, M. *The Isoquinoline Alkaloids*; Academic Press: New York, 1972; Chapter 15. (b) Cordell, G. A. *Introduction to Alkaloids: A Biogenetic Approach*; Wiley: New York, 1981; pp 422−423.

(7) Strictly speaking, a formal total synthesis of **1** has been achieved. In 1971, Shamma and Moniot (Shamma, M.; Moniot, J. L. *J. Chem. Soc. D* **1971**, *18*, 1065−1966) reported the biogenetically patterned conversion of the widespread quaternary aporphine (+)-magnoflorine (**i**) into taspine (**1**). For a synthesis of (±) magnoflorine, see: Tomita, M.; Kikkawa, I. *J. Pharm. Soc. Jpn.* **1957**, *77*, 195−199.



(8) For a report of model studies directed toward the synthesis of **1**, see: Scarpati, M. L.; Bianco, A.; Lo Scalzo, R. *Synth. Commun.* **1991**, *21*, 849−858.

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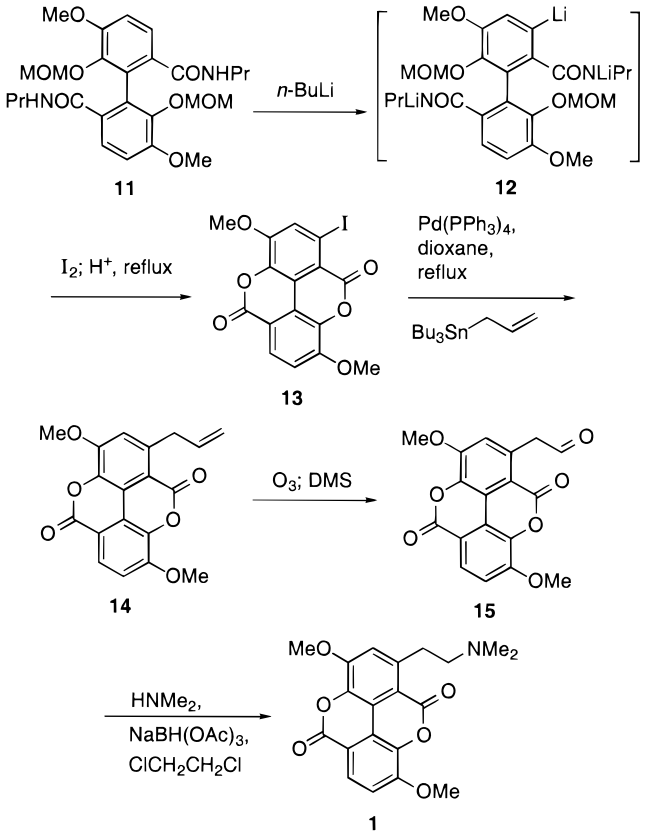
Published on Web 10/14/1998

Scheme 3. Side-Chain Attachment and Completion of the Synthesis of 1



of **9** with *n*-butyllithium (*n*-BuLi) and subsequent quenching with iodine supplied the desired 2-iodo-*N*-propylbenzamide **10**. Dimerization of **10** employing a classical Ullmann coupling reaction[12] utilizing activated[13] copper bronze gave the symmetrical homodimer **11** in 66% yield.[14]

Our synthetic plan for side-chain incorporation involved a second directed lithiation reaction, this time on dimer **11**, generating the aromatic anion at the desired position (**12**, Scheme 3) and combining it with side-chain-equivalent electrophiles to produce **2**-type molecules. The lithiation of dimer **11** worked well to give **12** (as judged by D_2O quenching studies); nonetheless, and despite considerable effort, we were unable to find a carbon-containing electrophile to serve as a simple side-chain synthon that could be directly attached to the dimer anion **12**.[15] Finally, as depicted in Scheme 3, the successful, but indirect, side-chain installation was accomplished by beginning with a Stille coupling between the iodo bislactone **13**[20] and allyltributyltin to generate the allyl bislactone **14** in 82% yield. Iodo bislactone **13** was obtained from an iodine quenching of anion **12** followed by a same-pot, acid-catalyzed double deprotection and lactonization in 61% overall yield from **11**. Ozonolysis of **14** supplied the aldehyde **15** in 57% yield. Reductive amination[21] of **15** with dimethylamine and sodium triacetoxyborohydride [$(NaBH(OAc)_3)$][22] gave taspine (**1**) in 75% isolated yield. Spectra of synthetic **1** were identical to those reported for the natural product. Synthetic and natural material[23] were also shown to be identical by direct comparison by using TLC co-spotting, ^{1}H NMR spiking, and mixture mp determination.

Conclusion. In summary, the first total synthesis of taspine (**1**) has been achieved. The synthesis is ac-

(9) Bodanszky, M. *Peptide Chemistry*: *A Practical Textbook*; Springer-Verlag: Berlin, 1988; pp 62−68.

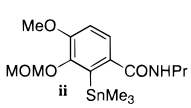
(10) (a) van Heerden, F. R.; van Zyl, J. J.; Rall, G. J. H.; Brandt, E. V.; Roux, D. G. *Tetrahedron Lett.* **1978**, 661−662. (b) For related applications, see: Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522−4524 and references therein.

(11) For a recent review, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

(12) For a review, see: Jukes, A. E. *Adv. Organomet. Chem.* **1974**, *12*, 215−322.

(13) Kleiderer, E. C.; Adams, R. *J. Am. Chem. Soc.* **1933**, *55*, 4219−4225.

(14) Other attempts to make dimer **11**, particularly palladium-catalyzed cross-coupling strategies involving the reaction between **10** and **ii** (prepared by reaction of **9** with BuLi then Me_3SnCl), were not successful, perhaps because of severe steric hindrance. For a leading reference to successful palladium-catalyzed biaryl couplings from this laboratory, see: Kelly, T. R.; Lee, Y.-J.; Mears, R. J. *J. Org. Chem.* **1997**, *62*, 2774−2781.



ii

(15) For a previous report of similar difficulties, see: Lovely, C. J.; Brueggemeier, R. W. *Tetrahedron Lett.* **1994**, *35*, 8735−8738. Electrophiles that failed to work include (a) β-chloro-*N*,*N*-dimethylethylamine ($Me_2NCH_2CH_2Cl$)[16] (prepared in situ from the HCl salt by addition of 1 equiv of BuLi); (b) *N*-tosylaziridine;[17] (c) a Weinreb-type amide,[18] 2-(dimethylamino)-*N*-methoxy-*N*-methylacetamide; (d) 1,2-dibromoethane (the Li in **12** is replaced by Br); and (e) ethylene oxide/CuI.[19]

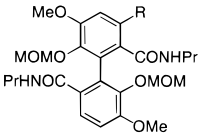
(16) For a review of synthetic applications of β-halo amines in medicinal chemistry, see: Miocque, M.; Duclos, J. P. *Chim. Ther.* **1969**, *4*, 363.

(17) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry*, *II*: *A Review of the Literature 1982−1995*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Editors-in-Chief; Padwa, A., Vol. Ed.; Pergamon Press: New York, 1996; Vol. 1A, pp 1−60.

(18) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. For a review, see: (b) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 17−40.

(19) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1984**, *49*, 3943−3949.

(20) Coupling reactions between iodide **iii** and allyltributyltin under various conditions only gave **iv** in low yields (<10%).



iii, R = I
iv, R = $CH_2CH{=}CH_2$

(21) For a review, see: Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 8, Chapter 1.2.

(22) (a) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535−536. For related applications, see: (b) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862 and references therein.

(23) Most papers reporting the isolation of natural taspine[2a,5a,26] state it to be optically inactive, but one publication[1a] reports an $[\alpha]^{24}_D$ of +7.6 (*c* 0.64, pyridine), a value that has been repeated in the secondary literature (*Dictionary of Natural Products*; Chapman & Hall: London, 1994; p 5338). In our view, a compound with the structure of **1** should not be capable of optical activity under ordinary circumstances. In support of that view, AM1 calculations using version 5.0 of Spartan (Wavefunction, Inc., Irvine, CA) indicate that the two carbocyclic rings in **1** are within 1° of coplanarity. We measured the $[\alpha]^{24}_D$ of a sample of natural taspine obtained from *Croton lechleri*[1b] generously provided by Dr. G. B. Hammond. In our measurement, we found an $[\alpha]^{24}_D$ of +0.9 (*c* 0.64, pyridine, heat to dissolve), but that value corresponds to a meter reading of only 0.006 on a Perkin-Elmer 241 polarimeter using a 1 dm cell (the meter reading fluctuated from 0.002 to 0.011; a control measurement using pure pyridine under the same conditions gave a less fluctuating meter reading of −0.001 to 0.002). While the ^{1}H NMR spectrum of the natural taspine provided by Dr. Hammond indicated the compound to be pure, we believe the optical rotation observed for taspine is due to contamination by a small amount of a highly optically active impurity. For whatever negative evidence is worth, as expected, we were unable to "resolve" synthetic (= racemic or achiral) taspine using the chiral NMR shift reagents europium tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorate] (Aldrich catalog no. 16,474-7) and europium tris[3-[(trifluoromethyl)hydroxymethylene]-(−)-camphorate] (Aldrich catalog no. 29,659-7).

complished in nine steps (9.6% overall yield) from commercially available **7** and provides an efficient route to **1** and, potentially, its analogues.

Experimental Section[24]

3-Hydroxy-4-methoxy-*N*-propylbenzenecarboxamide (8). Acid **7** (5.00 g, 29.7 mmol) was dissolved under N_2 in 200 mL of a 4:1 (v/v) mixture of anhydrous THF and HPLC-grade acetonitrile in a 500 mL round-bottomed flask. The solution was cooled to 0 °C (ice bath), followed by additions of dicyclohexylcarbodiimide (DCC; CAUTION: potential allergen) (6.20 g, 30.0 mmol) and *N*-hydroxysuccimide (3.50 g, 30.4 mmol) in single portions. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Formation of a white solid was observed as the temperature rose. Propylamine (3.30 mL, 40.1 mmol) was then added to the reaction mixture in one portion, and the reaction was heated at reflux for 2 h. After the reaction mixture was cooled to room temperature, the white solid (dicyclohexylurea) was removed from the crude mixture by vacuum filtration and the filtrate was subsequently washed with 2 × 50 mL of distilled water and then with 2 × 50 mL of saturated brine. The organic layer was then further dried over anhydrous $MgSO_4$ and filtered through a fritted funnel. Solvent removal in vacuo afforded a colorless solid [TLC (silica): R_f = 0.6, EtOAc], which was purified by silica gel flash column chromatography (75 mm × 300 mm, EtOAc) to afford 5.77 g (27.7 mmol, 93%) of the desired amide **8** as a colorless solid: mp 110−112 °C; IR (CH_2Cl_2) ν 3313, 2974, 2936, 2879, 1630, 1580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.4, 2.0 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.03 (br s, 1H), 5.81 (s, 1H), 3.93 (s, 3H), 3.39 (apparent q, J = 6.8 Hz, 2H), 1.62 (apparent sextet, J = 7.2 Hz, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 149.4, 145.6, 127.7, 119.3, 113.4, 110.2, 55.9, 41.7, 22.8, 11.3. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.23; H, 7.25; N, 6.75.

4-Methoxy-3-(methoxymethoxy)-*N*-propylbenzenecarboxamide (9). Phenol **8** (3.00 g, 14.3 mmol) was dissolved in 150 mL of distilled CH_2Cl_2. NaOH (0.850 g, 21.2 mmol) in 2.5 mL of distilled water was added in one portion at room temperature followed by 4.2 mL of Adogen 464. The reaction mixture was allowed to stir for 30 min at room temperature and was then cooled to 0 °C (ice bath). Chloromethyl methyl ether (MOMCl; CAUTION: cancer suspect agent) was then added dropwise over 1 h until reaction was complete [2.00 mL, 26.3 mmol, judged by TLC (silica): R_f = 0.56 for the desired product, and R_f = 0.37 for the starting material, 1:1 CH_2Cl_2/Et_2O]. The organic and aqueous phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase and organic extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo to leave behind a colorless solid. Purification by flash column chromatography (silica gel, 50 mm × 250 mm, 1:1 CH_2Cl_2/Et_2O) afforded the pure product **9** as a white crystalline solid (3.40 g, 94% yield): mp 85−86 °C; IR (CH_2Cl_2) ν 3326, 3087, 2961, 2936, 1633, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 2.0 Hz, 1H), 7.41 (dd, J = 8.0, 2.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.38 (br s, 1H), 5.20 (s, 2H), 3.86 (s, 3H), 3.46 (s, 3H), 3.33 (apparent q, J = 7.2 Hz, 2H), 1.57 (apparent sextet, J = 7.2 Hz, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 152.2, 146.0, 127.5, 121.4, 115.1, 110.8, 95.4, 56.2, 55.8, 41.6, 22.8, 11.3. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.85; H, 7.31; N, 5.29.

2-Iodo-4-methoxy-3-(methoxymethoxy)-*N*-propylbenzenecarboxamide (10). The starting material **9** (1.50 g, 5.92 mmol) was dissolved in 150 mL of anhydrous THF in a 250 mL round-bottomed flask. The solution was cooled with a −60 °C cooling bath under N_2, and *n*-butyllithium (8.70 mL, 1.5 M in pentane, 13 mmol) was added over 5 min; the mixture was allowed to stir for 2 h, after which time a solution of 3.30 g of I_2 (13.0 mmol) in 20.0 mL of anhydrous THF was added dropwise until the iodine color persisted (approximately 12.0 mL of the iodine solution, 7.8 mmol of iodine, was added over 1 min). The cooling bath was then removed, and the reaction was allowed to warm on its own to room temperature (over ca. 1 h). THF was removed on the rotary evaporator, and the residual solid was redissolved in 100 mL of CH_2Cl_2 and washed with two 50 mL portions of a saturated aqueous solution of $Na_2S_2O_3$; the organic layer was then dried over anhydrous $MgSO_4$. Subsequent removal of solvent in vacuo and purification by flash column chromatography (silica gel, 50 mm × 250 mm, 1:1 CH_2Cl_2/Et_2O) afforded 1.75 g (78%) of **10** (R_f = 0.63 for the desired product and R_f = 0.56 for the starting material, silica TLC, 1:1 CH_2Cl_2/Et_2O) as a white solid: mp 94−95 °C; IR (CH_2Cl_2) ν 3276, 3068, 2961, 1646, 1545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 5.82 (br s, 1H), 5.15 (s, 2H), 3.84 (s, 3H), 3.67 (s, 3H), 3.39 (apparent q, J = 7.2 Hz, 2H), 1.64 (apparent sextet, J = 7.2 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 152.6, 145.6, 136.1, 123.9, 112.0, 98.6, 92.1, 58.3, 55.9, 41.6, 22.5, 11.4. Anal. Calcd for $C_{13}H_{18}INO_4$: C, 41.18; H, 4.78; N, 3.69. Found: C, 40.93; H, 5.01; N, 3.58.

2,2′-Bis[4-methoxy-3-(methoxymethoxy)-*N*-propylbenzenecarboxamide] (11). Copper Bronze Activation. Commercial copper bronze (Aldrich Catalog No. 29,258-3) was activated following Kleiderer and Adams's procedure.[13] For a typical case, 2.50 g of copper bronze was treated with 25 mL of a 2% (w/v) solution of iodine in acetone at room temperature for 10 min. The gray-colored copper was then collected by vacuum filtration (open to the air) and subsequently stirred in 12.5 mL of a 1:1 acetone/HCl (12.0 N) mixture at room temperature for 10 min. It was filtered again and washed thoroughly with acetone. At this time, the copper bronze had a shiny brown color. It was dried in a vacuum desiccator (vacuum: ∼2 Torr) with P_2O_5 for 30 min and used immediately afterward.

Then, into a magnetically stirred, refluxing mixture of 1.20 g of freshly activated copper bronze and 20.0 mL of anhydrous DMF under nitrogen was added 1.05 g of **10** (2.77 mmol) in 20.0 mL of dry DMF via an addition funnel in a dropwise fashion over 1 h. The reaction mixture was then refluxed for another 2 h. An aliquot of reaction mixture was worked up by removing the solvent (DMF) with a vacuum pump (vacuum: ∼2 Torr) and redissolving the residue with CH_2Cl_2. TLC (silica, 9:1 dichloromethane/methanol, R_f = 0.55 and 0.80 for the desired product and the starting material, respectively) indicated that no starting material was left. The reaction mixture was then cooled to room temperature. The reaction mixture was filtered through Celite, and the Celite and solid were washed with DMF (2 × 10 mL). The combined filtrate and washes were evaporated to dryness under vacuum (∼2 Torr) to give a gray solid residue which was subsequently purified by flash column chromatography on silica gel (50 mm × 150 mm, 9:1 dichloromethane/methanol) to afford 463 mg (0.918 mmol, 66% yield) of the desired dimer **11** as a white solid: mp 148−149 °C; IR (CH_2Cl_2) ν 3270, 3074, 1646, 1596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 2H), 6.96 (t, J = 5.2 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.93 (d, J = 6.0 Hz, 2H), 4.77 (d, J = 6.0 Hz, 2H), 3.80 (s, 6H), 2.99 (dt, J = 5.2, 6.8 Hz, 4H), 2.81 (s, 6H), 1.11 (tq, J = 6.8, 7.2 Hz, 4H), 0.590 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 153.0, 143.2, 131.4, 129.0, 124.2, 111.5, 98.0, 56.1, 55.7, 41.2, 22.1, 11.1; HRMS calcd for $C_{26}H_{36}N_2O_8$ 504.2471, found 504.2468. Anal. Calcd for $C_{26}H_{36}N_2O_8$: C, 61.89; H, 7.19; N, 5.55. Found: C, 61.54; H, 7.26; N, 5.41.

1-Iodo-3,8-dimethoxy[1]benzopyrano[5,4,3-*cde*][1]benzopyran-5,10-dione (13). Dimer **11** (400 mg, 0.793 mmol) was dissolved under N_2 in 20.0 mL of dry THF in a 100 mL round-bottomed flask. The solution was cooled with a −60 °C cooling bath under nitrogen, and *n*-butyllithium (1.75 mL, 1.5 M in pentane, 2.6 mmol) was added over 5 min. The mixture was allowed to stir for 2 h at that temperature, after which a solution of 667 mg (2.63 mmol) of iodine in dry THF was transferred in 1 min via cannula into the reaction flask (5.0 mL of THF was used to dissolve the iodine and 2 mL of THF to rinse the flask and cannula, for a total volume of 7 mL of THF). The

(24) For most general experimental procedures, see: Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623−4633. 1,2-Dichloroethane was distilled from calcium hydride. Neutral alumina (activated, Brockmann I, ∼150 mesh) was purchased from Aldrich (catalog no. 19,997-4). For reactions monitored by alumina analytical TLC, neutral aluminum oxide plates were used. Ozone was generated using an OSMONICS OREC V5-O ozone generator (Phoenix Operations, Phoenix, AZ) and bubbled into the reaction mixture.

cooling bath was then removed, and the reaction was allowed to warm naturally to room temperature over ca. 1 h. The mixture was quenched with 10 mL of a 1:1 mixture of methanol and concd hydrochloric acid. The mixture was then heated at reflux for 10 h. A white solid [TLC (silica): $R_f = 0.77$ for the desired product (**13**) and $R_f = 0.32$ for the starting material (**11**), 20:1 CH_2Cl_2/methanol] started to precipitate during the refluxing. After being cooled to room temperature, the crude solid product was collected via vacuum filtration and was washed with three 10 mL portions of methanol followed by three 10 mL portions of CH_2Cl_2. Removal of residual solvent from the solid on a vacuum pump (~2 Torr) afforded 205 mg (0.483 mmol, 61%) of pure **13**: mp 320−324 °C dec; IR (KBr) ν 2930, 1740, 1589 cm^{-1}; ^1H NMR[25] (400 MHz, $CDCl_3$) δ 8.22 (d, $J = 8.8$ Hz, 1H), 7.89 (s, 1H), 7.33 (d, $J = 8.8$ Hz, 1H), 4.11 (s, 3H), 4.10 (s, 3H). Anal. Calcd for $C_{16}H_9IO_6$: C, 45.31; H, 2.14. Found: C, 45.38; H, 2.07.

3,8-Dimethoxy-1-(2-propenyl)[1]benzopyrano[5,4,3-*cde*]-[1]benzopyran-5, 10-dione (14). Tetrakis(triphenylphosphine)-palladium(0) (10.8 mg, 0.0934 mmol) and iodo lactone **13** (200 mg, 0.471 mmol) were weighed in a glovebox under N_2 into a 50 mL round-bottomed, three-necked flask equipped with a reflux condenser and rubber septa. The reaction vessel was subsequently removed from the glovebox and maintained under a nitrogen atmosphere. Allyltributyltin (175 μL, 0.564 mmol) was then introduced via a syringe in one portion to the catalyst and the starting material mixture followed by 20.0 mL of freshly distilled anhydrous 1,4-dioxane. The reaction flask was immersed in an oil bath that had been preheated to 120 °C, and the mixture was allowed to reflux for 14 h. After this period, the reaction vessel was cooled to room temprature. Removal of solvent in vacuo afforded a gray solid [TLC (silica): $R_f = 0.82$ for the desired product (**14**) and $R_f = 0.77$ for the starting material (**13**), 20:1 CH_2Cl_2/methanol]. Purification using flash column chromatography on silica gel (20:1 CH_2Cl_2/methanol) delivered 130 mg (0.384 mmol, 82%) of the desired product as a colorless solid. Recrystallization from CH_2Cl_2 supplied a needle-shaped crystalline sample for elemental analysis: mp 280−300 °C dec; IR (KBr) ν 1753, 1608 cm^{-1}; ^1H NMR[25] (400 MHz, $CDCl_3$) δ 8.20 (d, $J = 8.4$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 7.14 (s, 1H), 6.09 (m, 1H), 5.13 (m, 2H), 4.11 (m, 2H, partially hidden underneath aromatic methoxy peaks), 4.10 (s, 3H), 4.09 (s, 3H). Anal. Calcd for $C_{19}H_{14}O_6$: C, 67.45; H, 4.17. Found: C, 67.23; H, 4.39.

3,8-Dimethoxy-1-(2-oxoethyl)[1]benzopyrano[5,4,3-*cde*]-[1]benzopyran-5,10-dione (15). Allyl bislactone **14** (115 mg, 0.340 mmol) was dissolved in 200 mL of freshly distilled 1,2-dichloroethane (DCE) in a 250 mL round-bottomed flask purged with nitrogen. The reaction mixture was then cooled to −78 °C, and ozone was introduced into the reaction mixture until a faint blue color was observed. Dimethyl sulfide was then added (5.0 mL, 68 mmol, in one portion via syringe). The resulting mixture was allowed to stir at −78 °C for 1 h, at 0 °C for 1 h, and at room temperature for an additional 1 h. Volatiles were removed in vacuo, and the crude product was further purified by flash column chromatography (neutral alumina, activated, Brockmann I) using 50:1 dichloromethane/methanol to give 66.2 mg of pure aldehyde **15** (0.194 mmol, 57%, $R_f = 0.63$ for the desired product and $R_f = 0.96$ for the starting material, alumina TLC) as a white solid. During the melting point measurement, the colorless sample started to darken above 120 °C and decomposed without melting between 275 and 280 °C: IR (KBr) ν 2923, 1746, 1602 cm^{-1}; ^1H NMR[25] (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.13 (d, $J = 8.8$ Hz, 1H), 7.62 (d, $J = 8.8$ Hz, 1H), 7.56 (s, 1H), 4.35 (s, 2H), 4.07 (s, 3H), 4.06 (s, 3H); HRMS calcd for $C_{18}H_{13}O_7$ (M + H) 341.0661, found 341.0657. Anal. Calcd for $C_{18}H_{12}O_7$: C, 63.53; H, 3.55. Found: C, 63.26; H, 3.42.

1-[2-(Dimethylamino)ethyl]-3,8-dimethoxy[1]-benzopyrano[5,4,3-*cde*][1]benzopyran-5,10-dione (Taspine, 1). Aldehyde **15** (45.0 mg, 0.132 mmol) was suspended in 40 mL of freshly distilled DCE in a 100 mL round-bottomed, three-necked flask under a nitrogen atmosphere at room temperature, and dimethylamine (70 μL of a 2.0 M solution in THF, 0.14 mmol) was added. The resulting mixture was a yellow-greenish cloudy suspension. Solid sodium triacetoxyborohydride (Aldrich Catalog no. 31639-3) was gradually added over 10 min to the reaction mixture. After a total of 33.5 mg (0.158 mmol) of $NaBH(OAc)_3$ had been added, the reaction mixture became clear and no starting material remained, as judged by TLC using an alumina plate (20:1 CH_2Cl_2/methanol, $R_f = 0.70$ for desired product and $R_f = 0.98$ for the starting material). The solvent was removed in vacuo to give a yellow solid, which was purified by flash column chromatography (neutral alumina, activated, Brockmann I, 20:1 CH_2Cl_2/methanol) to afford 36.7 mg of the desired product as a white solid (0.0994 mmol, 75% yield): mp 372−374 °C dec; (lit.[1a,5a] mp of the naturally derived taspine) 370 °C dec; mp of a mixture of synthetic and natural taspine (ca. 1:1) 369−372 °C dec; IR[5c,26] (KBr) ν 2948, 1740, 1602 cm^{-1}; ^1H NMR[1a,3a,b] (400 MHz, $CDCl_3$) δ 8.21 (d, $J = 8.8$ Hz, 1H), 7.31 (d, $J = 8.8$ Hz, 1H), 7.20 (s, 1H), 4.10 (s, 6H), 3.53 (t, $J = 7.6$ Hz, 2H), 2.68 (t, $J = 7.6$ Hz, 2H), 2.41 (s, 6H); ^{13}C NMR[3a,b] (100 MHz, $CDCl_3$) δ 158.7, 157.7, 151.2, 151.0, 144.3, 137.9, 136.8 126.9, 119.1, 118.5, 116.5, 113.6, 111.6, 109.2, 60.3, 56.6, 56.5, 45.3, 33.0; HRMS calcd for $C_{20}H_{20}NO_6$ (M + H) 370.1291, found 370.1282. Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.20; H, 5.06; N, 3.64.

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(25) Because of low solubilities, ^{13}C NMR spectra of compounds **13**−**15** were not recorded.

(26) Talapatra, B.; Chaudhuri, P. K.; Talapatra, S. K. *Phytochemistry* **1982**, *21*, 747−750.