ORGANIC LETTERS

2000
Vol. 2, No. 21
3269−3271

Synthesis, Utility, and X-ray Crystal Structure of Novel Complexes of Baccatin III with Imidazole and 2-Propanol

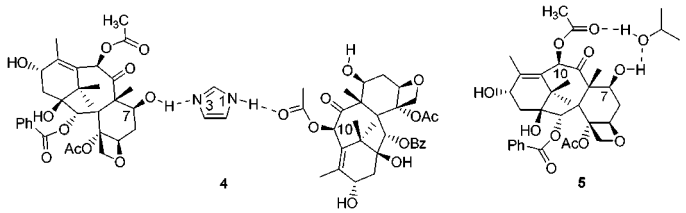
Frank S. Gibson,* Jianmei Wei, Purushotham Vemishetti, Qi Gao,[†] and John L. Dillon*,[‡]

Bristol-Myers Squibb Company, Process Exploration Labs, Technical Operations Development, P.O. Box 4755, Syracuse, New York 13221-4755, and Analytical Research and Development, Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut 06492

john.dillon7@honeywell.com

Received July 14, 2000

ABSTRACT



Baccatin III forms crystalline complexes 4 and 5 with imidazole and 2-propanol, respectively. These compounds are useful in the purification of baccatin III from mixtures of taxanes derived from plant-cell fermentation.

The baccatin III core is the central structural feature of TAXOL® (paclitaxel) **1**, a diterpenoid natural product which has become one of the most important anticancer therapies of recent times.[1] Taxanes lacking a phenylisoserine side chain at the C-13 position, such as 10-deacetyl baccatin III (10-DAB) **2** and baccatin III **3**, show a much lower cytotoxic response to cancer cells and a different mechanism of action.[2] These compounds are, however, useful intermediates for the semisynthesis of paclitaxel and docetaxel.[3] Since the semisynthesis of paclitaxel requires acetylation of the C-10 hydroxyl group, baccatin III **3** represents a more efficient starting material than **2** for this process (Figure 1).

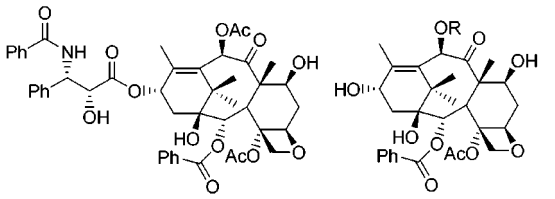


Figure 1. Structures of TAXOL, 10-DAB, and baccatin III.

During the course of our synthetic studies with taxanes, we have discovered that baccatin III **3** selectively forms novel, crystalline complexes, **4** and **5**, with imidazole and 2-propanol (Figure 2). These compounds allow for a simple means of purification of **3** from complex mixtures of taxanes derived from plant-cell fermentation. In this Letter, we report

[†] Wallingford, CT. To whom correspondence regarding X-ray crystal structures should be addressed.

[‡] Present address: Honeywell Co. Pharmaceutical Fine Chemicals, 20 Peabody St., Buffalo, NY 14210.

(1) (a) Georg, G. I.; Chen. T. T.; Ojima, I.; Vyas, D. M. *Taxane Anticancer Agents*, ACS Symp. Ser.; American Chemical Society: Washington, DC, 1995; p 583. (b) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1.

(2) Pengsuparp, T.; Kingston, D. G. I.; Neidigh, K. A.; Cordell, G. A.; Pezzuto, J. M. *Chem.-Biol. Interact.* **1996**, *101*, 103.

10.1021/ol006332q CCC: $19.00
Published on Web 09/19/2000

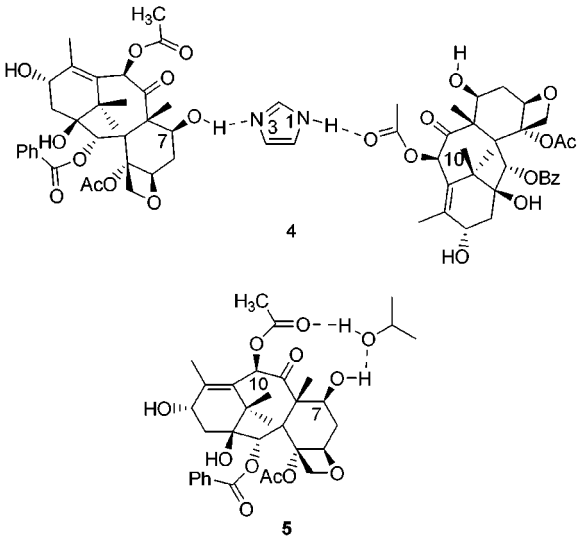


Figure 2. Crystalline complexes of baccatin III with imidazole, **4**, and 2-propanol, **5**.

the preparation, utility, and X-ray crystal structure of these compounds.

Treatment of a solution of baccatin III in dichloromethane with imidazole produced a crystalline solid. Single-crystal X-ray diffraction established the compound to be **4**, a 1:1 polymeric complex of baccatin III and imidazole which was isolated in 89% yield.

The intermolecular interaction involves two hydrogen bonds (Figure 3). One H-bond is between N-1 of imidazole and the carbonyl oxygen of the C-10 acetyl group of baccatin III (159.0°, O···N = 2.643 Å, H···N = 1.743 Å). The second H-bond exists between N-3 of imidazole and the C-7 hydroxyl group of another baccatin III molecule (154.0°, N···O = 2.898 Å, H···O = 2.000 Å). One-fourth molar equivalent of water completes the complex with hydrogen bonds at O-1 and O-13 of baccatin III.[4]

Formation of the complex was also possible in other common organic solvents such as ethyl acetate or acetone. The complex was found to be stable to recrystallization from acetonitrile. Paclitaxel did not form a similar complex.

In marked contrast to the imidazole complex that involves intermolecular interactions, recrystallization of baccatin III with dichloromethane-2-propanol leads to the formation of a 1:1 complex, **5**, consisting of intramolecular hydrogen bonds between baccatin III and 2-propanol (Figure 4). The hydroxyl group of 2-propanol cross-links the C-7 hydroxyl group, O7−H···O(O···O = 2.645 Å), and the carbonyl oxygen of the C-10 acetyl group of baccatin III, H−O···O10 (O···O = 2.734 Å). Comparison of the crystal structure to imidazole complex **4** reveals that the two complexes are isomorphous with the 2-propanol molecules found in infinite linear channels along the crystallographic *a*-axis.[5]

The complexes **4** and **5** were found to have utility in nonchromatographic purification and isolation of baccatin III from solutions containing a myriad of other taxanes derived from plant-cell fermentation.[6] When imidazole was added to a solution of baccatin III obtained by butyl acetate extraction of a broth derived from plant cell fermentation, and containing a variety of taxanes, a precipitate was formed which was shown to be **4** of good quality. After filtration, the solid complex was readily broken and the baccatin III recovered in near quantitative yield by aqueous extraction of a solution of **4** dichloromethane. In this manner the baccatin III partitions to the dichloromethane and imidazole to the aqueous phase. Separation of the organic layer and removal of solvent followed by recrystallization afforded baccatin III of high purity. Similary, concentration of the butyl acetate extract obtained as described above to dryness and dissolution in hot 2-propanol led to the formation of a baccatin III-2-propanol complex of good quality.

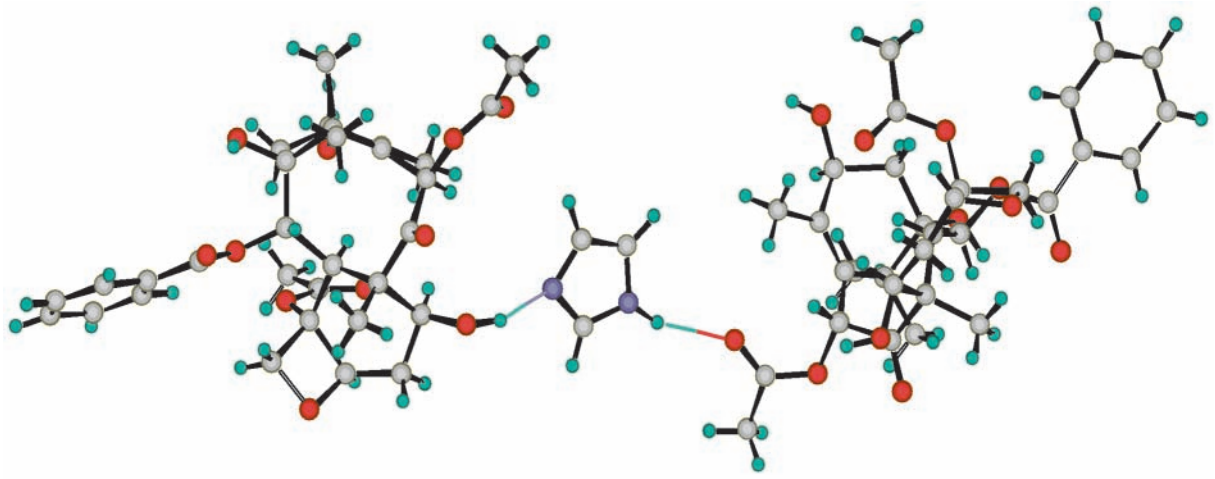


Figure 3. X-ray crystal structure of baccatin III−imidazole complex, **4**.

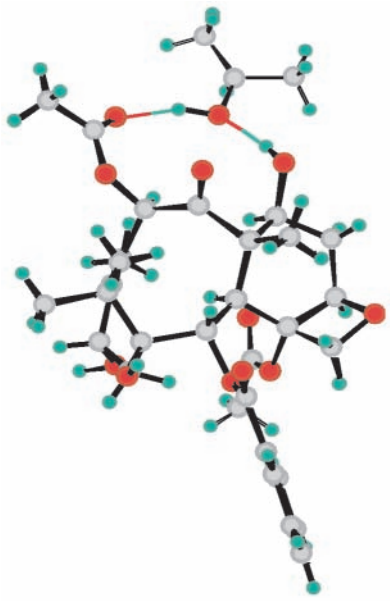


Figure 4. X-ray crystal structure of baccatin III−2-propanol complex, **5**.

In summary, novel complexes of baccatin III with imidazole and 2-propanol have been described along with their use in the recovery and purification of baccatin III from solutions containing other taxanes. Determination of the ability of baccatin III to form complexes with other compounds as well as their solution properties and reactivity is under investigation in our laboratories.

Supporting Information Available: Experimental procedures for preparation of baccatin III−imidazole and baccatin III−2-propanol complexes, purification of baccatin III from plant cell fermentation broth, and X-ray crystal coordinates for **4** and **5**.

OL006332Q

(3) (a) *TAXOL: Science and Applications*; Suffness, M., Ed.; CRC Press: 1995. (b) Denis, J.-N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. (c) Holton, R. A. U.S. Patent 5,015,744, 1992. (d) Holton, R. A. U.S. Patent 5,136,060, 1992. (e) Holton, R. A. U.S. Patent 5,229,526, 1993. (f) Kingston, D. G. I.; Chaudhary, A. G.; Guanatilaka, A. A. L.; Middleton, M. L. *Tetrahedron Lett.* **1994**, *35*, 4483. (f) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M. *Tetrahedron* **1992**, *48*, 6985. (g) Ojima, I.; Sun. C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. D. *Tetrahedron* **1993**, 4149.

(4) A crystal of **4** obtained as a colorless thick plate from acetonitrile measuring 0.10 mm × 0.35 mm × 0.42 mm was used for X-ray diffraction measurements. Crystal data: $C_{31}H_{38}O_{11}-C_3H_4N_2 \cdot 0.25H_2O$, orthorhombic, space group $P2_12_12$, $a = 9.2771(4)$ Å, $b = 41.215(2)$ Å, $c = 8.5788(4)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 883.7(2)$ Å^3, $Z = 4$, $d_x = 1.325$ g cm^{-3}. A total of 3894 independent reflections were measured of which 3266 were observed with $|I| \geq 3\sigma$.

(5) A crystal of **5** obtained as an unstable colorless plate from dichoromethane−2-propanol measuring 0.20 mm × 0.30 mm × 0.45 mm was used for X-ray diffraction measurements. Crystal data: $C_{31}H_{38}O_{11}-C_3H_8O$ orthorhombic, space group $P2_12_12$, $a = 9.3975(3)$ Å, $b = 41.736(2)$ Å, $c = 8.5401(3)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 883.7(2)$ Å^3, $Z = 4$, $d_x = 1.284$ g cm^{-3}. A total of 3684 independent reflections were measured of which 3469 were observed with $|I| \geq 3\sigma$. (b) The authors have deposited atomic coordinates for structure **4** and **5** with the Cambridge Crystallographic Data Center. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 IEZ, U.K.

(6) (a) Bringi, Venkataraman; Kadkade, P. G.; Kane, J. E.; Prince, C. L.; Roach, B.; Schubmehl, B. F. U.S. Patent 5,407,816. (b) Cuside, R. M.; Palazo, J.; Navia-Osorio, A.; Bonfil, M.; Morales, C.; Pinol, M. T. *Plant Sci.* **1999**, *146*, 101.