

Semisynthesis of New D-seco-C-nor-Taxane Derivatives Containing a Polyfunctionalized Furanosyl or Cyclopentenyl or Cyclopentyl C-Ring

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Received December 18, 2007



The synthesis of new D-seco-C-nor-taxane derivatives in which the D-ring has been deleted and the C-ring has been transformed into a new pentatomic ring, i.e., the polyfunctionalized tetrahydrofuranosyl and cyclopentenyl or cyclopentyl ring, was performed starting from baccatin III derivatives. The synthetic strategy adopted took advantage of the oxetane ring opening and disconnection of the C_4-C_5 bond, followed by an intramolecular condensation. The formation of furanosyl or cyclopentyl rings is strictly dependent on the presence of unprotected or protected oxygen at C-7 in the starting material. The reactions proceeded with good diastereoselectivity with control of the stereochemistry of one or two stereocenters.

Introduction

The modification of biological active scaffolds is one of the useful synthetic strategies aimed at finding new derivatives characterized by improved or modified activity. This is especially true for complex molecules containing many stereocenters. In many cases, the starting pharmacophore belongs to the class of natural compounds from which, by simple modifications such as the functionalization of pre-existing substituents or the introduction of a particular functional group, new compounds are developed which are characterized by improved activity, lower toxicity, or, for example, in the case of anticancer drugs, activity toward multidrug resistance (MDR).¹

Taxane derivatives, such as the natural product paclitaxel (Taxol, **1a**) and its semisynthetic analogue docetaxel (Taxotere,

1b) (Figure 1), two important anticancer agents useful for the treatment of breast, ovarian, and nonsmall cell lung cancers and also active against prostate cancer,² have been extensively investigated in order to develop improved analogues.³ Extensive SAR studies on the above compounds have been performed,³ including modifications of functional groups and the side chain.⁴ Our recent research has dealt with the modification of the C-14 position, leading to compounds with increased biological activity.⁵

Studies of the tetracyclic core (D-ring) of paclitaxel have been included in attempts to determine its importance in the interaction with tubulin. Transformations of the oxetane ring include substitution of the oxygen atom with other heteroatoms,⁶ its removal (D-modified or D-seco compounds), or its transformation to a cyclopropyl ring (5(20)-deoxydocetaxel).⁷ Contrary

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 ⁽a) Azerad, R. Biocatalysis in the Pharmaceutical and Biotechnology Industries; Patel, R. N., Ed.; CRC Press LLC: Boca Raton, FL, 2007; pp 273– 297. (b) Efange, S. M. N. Adv. Phytomed. 2002, 1, 61–69. (c) Yu, D. Zhongguo. Yixue Kexueyuan Xuebao 2002, 24, 335–338; Chem. Abstr. 2003, 139, 285308.
 (2) (a) Rowinsky, E. K. Annu. Rev. Med. 1997, 48, 353–374. (b) Crown, J.; O'Leary, M. Lancet 2000, 355, 1176–1178.

to previous reports, the D-ring is not required for the tubulin polymerizing activity of taxoids, and some of the above compounds have a strong microtubule-stabilizing activity.^{7g,h}

Concerning the C-ring, the most interesting compounds are the C-seco derivatives like **2** (Figure 1), which possess antimetastatic and cytostatic activity and low toxicity.⁸ New C-seco compounds were recently synthesized as antituberculosis agents.^{8c} Studies on structural modification of the C-ring by cleavage of the C₆–C₇ or C₇–C₈ bonds have also been performed, and interesting compounds were obtained through intramolecular reactions.^{9,7c} Recently, the synthesis of a new C,D-seco-taxoid was achieved by disconnection of the C₄–C₅ bond.¹⁰

The above research suggests that modification of the east region is very important, and in some cases improved properties and provided compounds that possess higher activity, better solubility, activity against MDR tumors, etc.

Considering these results, we planned to study a major transformation of the east region. These studies led to the preparation of new D-seco-C-nor derivatives, in which the D-ring has been deleted and the C-ring has been transformed into a new pentatomic ring, either a polyfunctionalized tetrahydrofuranosyl ring (compounds 12 and 13; Scheme 2), a cyclopentenyl (compounds 16 and 17; Scheme 3), or a cyclo-

(4) Chen, J.; Kuznetsova, L. V.; Ungreanu, I. M.; Ojima, I. In *Enantioselective* Synthesis of β -Amino Acids, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2005; pp 447–476.

(5) (a) Baldelli, E.; Battaglia, A.; Bombardelli, E.; Carenzi, G.; Fontana, G.; Gambini, A.; Gelmi, M. L.; Guerrini, A.; Pocar, D. J. Org. Chem. 2003, 68, 9773–9779. (b) Baldelli, E.; Battaglia, A.; Bombardelli, E.; Carenzi, G.; Fontana, G.; Gelmi, M. L.; Guerrini, A.; Pocar, D. J. Org. Chem. 2004, 69, 6610–6616.
(c) Baldelli, E.; Battaglia, A.; Bombardelli, E.; Carenzi, G.; Fontana, G.; Gelmi, M. L.; Guerrini, A.; Pocar, D. J. Org. Chem. 2004, 69, 6610–6616.
(c) Baldelli, E.; Battaglia, A.; Bombardelli, E.; Carenzi, G.; Fontana, G.; Gelmi, M. L.; Guerrini, A.; Pocar, D. J. Org. Chem. 2004, 67, 6610–6616.
(c) Baldelli, E.; Battaglia, A.; Bombardelli, E.; Carenzi, G.; Fontana, G.; Gelmi, M. L.; Guerrini, A.; Pocar, D. PCT Int. Appl. PIXXD2 WO 2004024706 A2 20040325, 2004; Chem. Abstr., 2004, 140, 287557. (d) Battaglia, A.; Baldelli, E.; Bombardelli, E.; Carenzi, G.; Fontana, G.; Gelmi, M. L.; Guerrini, A.; Pocar, D. Tetrahedron 2005, 61, 7727–7745.

(6) (a) Fenoglio, I.; Nano, G. M.; Vander Velde, D. G.; Appendino, G. *Tetrahedron Lett.* **1996**, *37*, 3203–3206. (b) Marder-Karsenti, R.; Dubois, J.; Bricard, L.; Guénard, D.; Guéritte-Voegelein, F. J. Org. Chem. **1997**, *62*, 6631–6637. (c) Gunatilaka, A. A. L.; Ramdayal, F. D.; Sarragiotto, M.; Kingston, D. G. I.; Sackett, D. L.; Hamel, E. J. Org. Chem. **1999**, *64*, 2694–2703. (d) Merckle', L.; Dubois, J.; Place, E.; Thoret, S.; Guéritte, F.; Guénard, D.; Poupat, C.; Ahond, A.; Potier, P. J. Org. Chem. **2001**, *66*, 5058–5065.



FIGURE 1. Taxane derivatives.

pentyl (compounds **21** and **22**; Scheme 4). The key synthetic strategy was the sequence of oxetane ring opening, disconnection of the C_4-C_5 bond, and intramolecular condensation. The cytotoxic activity of the above compounds was evaluated against H460 cells.

Results and Discussion

Our starting materials for the preparation of the new compounds were baccatin III (3a) and the corresponding 7-TES derivative 3b, which were first transformed into D-seco compounds 4a and 4b by opening of the oxetane ring (Scheme 1).

The oxetane ring opening was extensively studied by Chen et al.¹¹ and Liang et al.,^{9c} who found that the substitution pattern on the starting material, the choice of the Lewis acid, and the choice of quenching method determine both the ring A contraction and the regiochemistry of the acetoxy group which can be linked at C-20 or at C-5 when the oxetane ring is opened. Since it has been reported that tin tetrachloride (SnCl₄) does not induce transposition of ring A,¹¹ we selected this Lewis acid to obtain the 20-OAc-4,5-dihydroxy derivatives **4a**,**b**.

The reaction was first studied starting from the (triethylsilyl) derivative **3b** using SnCl₄ (1.1 equiv) in CH₂Cl₂ at 0 °C (10 min). TLC analysis showed the presence of two compounds (3:1, ¹H NMR analysis), which were isolated by column chromatography on silica gel, corresponding to **4b** (65%) and **5b** (29%). When the same reaction was quenched with aqueous NaHCO₃ (5%, 30 min, 0 °C), the transformation of **5b** into the 20-OAc derivative **4b** appeared to be quantitative (TLC analysis), but when the reaction mixture was chromatographed compound **4b** was isolated in 80% yield, together with **5b** (16%). The ¹H NMR spectrum of compound **5b** showed the presence of trace amounts of a second stereoisomeric 5-OAc derivative.

^{(3) (}a) Suffness, M.; Cordell, G. A. In *The Alkaloids. Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 25, pp 3–355. (b) Blechert, S.; Guenard, D. In *The Alkaloids. Chemistry and Pharmacology*. Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, pp 195–238. (c) Kingston, D. G. I. *Pharmacol. Ther.* 1991, 52, 1–34. (d) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. Prog. Chem. Org. Natl. Prod. 1993, 61, 1–188. (e) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. Angew. Chem., Int. Ed. Engl. 1994, 33, 15–44. (f) Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds. Taxane Anticancer Agents: Basic Science and Current Status; ACS Symposium Series; American Chemical Society: Washington, DC, 1995; 583, pp 1–353. (g) Suffness, M. Taxol Science and Application; Suffness, M., Ed.; CRC Press: New York, 1995; pp 317–375. (h) Guéritte, F. Curr. Pharm. Des. 2001, 7, 1229–1249. (i) Kingston, D. G. I.; Jagtap, P. J.; Yuan, H.; Samala, L. In Progress in the Chemistry of Organic Natural Products; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer-Verlag: Wien & New York, 2002; Vol. 84, pp 53–225. (j) Ganesh, T.; Yang, C.; Norris, A.; Giaanakakou, P.; Alcaraz, A. A.; Lakdawala, A. S.; Snyder, J. P.; Kingston, D. G. I. J. Med. Chem. 2007, 50, 713–725.

^{(7) (}a) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. J. Org. Chem. 1991, 56, 5114–5119. (b) Dubois, J.; Thoret, S.; Guéritte, F.; Guénard, D. Tetrahedron Lett. 2000, 41, 3331–3334. (c) Barboni, L.; Datta, A.; Jutta, D.; Georg, G. I.; Vander Velde, D. G.; Himes, R. H.; Wang, M.; Snyder, J. P. J. Org. Chem. 2001, 66, 3321–3329. (d) Beusker, P. H.; Veldhuis, H.; Van den Bossche, B. A. C.; Scheeren, H. W. Eur. J. Org. Chem. 2001, 1761–1768. (e) Beusker, P. H.; Veldhuis, H.; Birinkhorst, J.; Hetterscheid, D. G. H.; Feichter, N.; Bugaut, A.; Scheeren, H. W. Eur. J. Org. Chem. 2003, 689–705. (f) Deka, V.; Dubois, J.; Thoret, S.; Guéritte, F.; Guénard, D. Org. Lett. 2003, 5, 5031–5034. (g) Barboni, L.; Giarlo, G.; Ricciutelli, M.; Ballini, R.; Georg, G. I.; Vander Velde, D. G.; Himes, R. H.; Wang, M.; Lakdawala, A.; Snyder, J. P. Org. Lett. 2004, 6, 461–464. (h) Thoret, S.; Guéritte, F.; Guénard, D.; Dubois, G. Org. Lett. 2006, 8, 2301–2304.

^{(8) (}a) Appendino, G.; Danieli, B.; Jakupovic, J.; Belloro, E.; Scambia, E.; Bombardelli, E. *Tetrahedron Lett.* **1997**, *38*, 4273–4276. (b) Appendino, G.; Noncovich, A.; Bettoni, P.; Dambruoso, P.; Sterner, O.; Fontana, G.; Bombardelli, E. *Eur. J. Org. Chem.* **2003**, 4422–4431. (c) Huang, Q.; Kirikae, F.; Kirikae, T.; Pepe, A.; Amin, A.; Respicio, L.; Slayden, R. A.; Tonge, P. J.; Ojima, I. *J. Med. Chem.* **2006**, *49*, 463–466.

^{(9) (}a) Magri, N. F.; Kingston, D. G. I. J. Org. Chem. 1986, 51, 797–802.
(b) Liang, X.; Kingston, D. G. I. Tetrahedron Lett. 1995, 36, 7795–7798. (c) Liang, X.; Kingston, D. G. I.; Long, B. H.; Fairchild, C. A.; Johnston, K. A. Tetrahedron 1997, 53, 3441–3456. (d) Yuan, H.; Kingston, D. G. I.; Long, B. H.; Fairchild, C. A.; Johnston, K. A. Tetrahedron 1999, 55, 9086–9100. (e) Nikolakakis, A.; Caron, G.; Cherestes, A.; Sauriol, F.; Mamer, O.; Zamir, L. O. Biorg. Med. Chem. 2000, 8, 1269–1280.



^{*a*} Reaction conditions: (i) SnCl₄, CH₂Cl₂, 0 °C; (ii) aqueous NaHCO₃ (5%, 0 °C); (iii) SiO₂; (iv) Pb(OAc)₄, CH₂Cl₂, 0 °C; (v) **8a**: MeCN/Py (1:1), Py •HF, 0 °C; (vi) **8b**: Py, 0 °C, MeCN.





^a Reaction conditions: (i) DMAP, DCC, CH₂Cl₂, 25 °C; (ii) NaBH₄, EtOH, -20 °C; (iii) CH₂Cl₂, 0 °C, 0.01 M AcCl in MeOH.

In agreement with the above results, reaction of compound **3a** with $SnCl_4$ in CH_2Cl_2 at 0 °C gave the regioisomers **4a** (70%) and **5a** (10%) after quenching of the reaction mixture with NaHCO₃ and after column chromatography.

The presence of the diol function at C_4-C_5 in compounds 4 made it possible to open the C-ring by an oxidative process. Different oxidants were tested (NaIO₄, HIO₄, Pb(OAc)₄). Lead tetraacetate was the most efficient reagent in CH₂Cl₂ at 0 °C (30 min), and the new derivative 6 (84%) was directly obtained from 4a (Scheme 1). It is assumed that the C₄-C₅ bond was first cleaved to give the intermediate 7a (not isolated), followed by direct cyclization to hemiacetal 6 by reaction of the hydroxy group with the keto group. A single diastereomer, characterized by the cis stereochemistry between the two carbon substituents and the *S* absolute configuration at the new generated C-4 stereocenter, was formed (see NMR discussion, Supporting Information).

This result is different from a report in the literature¹¹ concerning the oxidation of a 4,5-dihydroxy-20-acetoxypaclitaxel derivative, which maintained the unchanged C-ring although the authors also cited the formation of a byproduct characterized by the presence of a tetrahydrofuran ring. With the aim to isolate an intermediate structure **7**, the same oxidative protocol was applied to **4b**, which gave the expected C,D-seco compound **7b** in 95% yield.

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Compound **7b** is a very interesting intermediate because it explains the formation of **6** from **7a** when O-7 is deprotected and because it is characterized by the presence of polyfunctionalized chains linked to the C-ring. This suggested the possibility of obtaining new carbocyclic D-seco-C-nor derivatives containing a cyclopentyl ring by taking advantage of an intramolecular aldol condensation reaction.

By treating compound **7b** with Py•HF in a mixture of MeCN/ Py as the solvent (24 h, 0 °C then 25 °C) to deprotect the oxygen atom at C-7, neither derivative **7a** nor the furanoside **6** were formed, and the new compound **8a** (88%), containing a cyclopentyl C-ring, was isolated.

In principle, two different regioisomeric aldol products could be formed, the compounds deriving from the condensation of the carbon α to the keto group on the aldehyde function or that of the carbon α to the aldehyde group on the keto function. The presence of the aldehyde function (¹H and ¹³C NMR analyses, see the Supporting Information) supported the assigned structure. The reaction occurs with good diastereoselectivity,



^a Reaction conditions: (i) DMAP, DCC, CH₂Cl₂, 25 °C; (ii) NaBH₄, EtOH, -20 °C; (iii) CH₂Cl₂, 0 °C, 0.01 M AcCl in MeOH.

SCHEME 4. Synthesis of D-seco-C-nor Derivatives 21 and 22 Containing a Cyclopentyl C-Ring^a



^{*a*} Reaction conditions: (i) DMAP, DCC, CH₂Cl₂, 25 °C; (ii) Py, MeCN, 0 °C, then Py+HF; (iii) NaBH₄, EtOH, -20 °C; (iv) CH₂Cl₂, 0 °C, 0.01 M AcCl in MeOH.

and a mixture of isomers (80:10:7:3; ¹H NMR analysis)¹² was formed in which isomer **8a** is the main one. The purification of the mixture of isomers by semipreparative HPLC (reversed phase, MeCN/H₂O, 1:1) resulted in an equilibration between the isomers due to a retro-condensation reaction operative in aqueous solution, even if the ¹H NMR spectrum in CDCl₃ of the main fraction showed only a trace amount of a second isomer (see HPLC and ¹H NMR data, Supporting Information). NMR studies on the more abundant isomer showed that it is characterized by a cis stereochemistry between the two carbon residues on the cyclopentyl ring (see the Supporting Information).

Considering these results, it must be assumed that the condensation reaction to give the cyclopentyl ring is brought about by pyridine or by the Py•HF reagent (see discussion) and that the condensation reaction is faster than the desilylation reaction, thus preventing the formation of the furanoside ring.

The ability of pyridine alone to induce the condensation reaction was also evaluated, and compound **7b** was treated with pyridine in MeCN (1:3) at 0 °C. In this case, the cyclization reaction was slower (3 days), but the expected cyclopentyl derivative **8b**¹² (98%) was isolated as a mixture of diastereomers in the same range of distribution (77:11:8:4; ¹H NMR analysis) in which the main isomer is characterized by the same

stereochemistry as 8a (Scheme 1). Attempts to separate the isomers by HPLC failed as shown for 8a (see HPLC and ¹H NMR data, Supporting Information).

The homoserine acid (mixture of diastereomers at the acetal stereocenter) was then linked at OH-13 of both compounds 6 and 8a. The reaction of compound 6 with the protected homoserine chain 9 (Scheme 2), operating in CH_2Cl_2 in the presence of N,N-dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide (DCC), afforded compound 10 (96%, diastereomeric mixture). Deprotection of the side chain (0.01 M AcCl in MeOH, CH₂Cl₂) gave a mixture of diastereomers 12 (40%; 87:13) in which the main one is indicated in Scheme 2 and is characterized by the same stereochemistry of the compound 6. Since the starting baccatin derivative 6 was a single stereomer, the formation of diastereomers 12 was ascribed to the partial epimerization at C-4 of the hemiacetal function. This behavior made impossible the purification by semipreparative HPLC. In fact, a dynamic equilibrium was detected by performing HPLC analyses at different temperature (see the Supporting Information).

The aldehyde function of **10** was reduced with NaBH₄ in EtOH at -20 °C (1 h), and the more stable hydroxy derivative **11** (45%, diastereomeric mixture) was prepared. Deprotection of the side chain gave pure compound **13** (63%) (Scheme 2).

A similar synthetic protocol was applied to **8a** (Scheme 3), which was made to react with **9** using the same reaction conditions reported above. Interestingly, in this case compound

⁽¹⁰⁾ Ferjancic, Z.; Matovic, R.; Cekovic, Z.; Jiang, Y.; Snyder, Y. P.; Trajkovic, V.; Saicic, R. N. *Tetrahedron* **2006**, *62*, 8503–8514.

⁽¹¹⁾ Chen, S.-H.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805-2828.

14 (61%), containing the unsaturated aldehyde function, was obtained by dehydration of the aldol product promoted by DCC.

Reduction of the aldehyde group of **14** with NaBH₄ gave **15** in 50% yield. Deprotection of the side chain of both **14** and **15** using the above reaction conditions afforded compound 16^{12} (37%, mixture of isomers, 83:17) and alcohol **17**¹² (90%; mixture of isomers, 89:11), respectively.

Attempt to separate by semipreparative HPLC isomers of **16** failed because of their degradation. Instead, the pure isomer **17** indicated in Scheme 3 was isolated in pure form.

NMR experiments (see the Supporting Information) on compound **16** confirmed the presence of both the olefin proton and the acetal function formed by reaction of methanol with the formyl group.

In an attempt to avoid water elimination and to verify if the presence of the side chain could influence the stereochemistry of the stereocenters generated in the condensation process a different synthetic strategy depicted in Scheme 4 was carried out.

Compound **7b** was first functionalized at OH-13 with the protected homoserine acid **9** to give **18** (75%, mixture of diastereomers) (Scheme 4).

The condensation reaction together with the deprotection of OH-7 was achieved using a "one pot" procedure starting from 18 and operating in a mixture of MeCN and pyridine (1:1) at 0 °C (10 min) to which a solution of Py•HF was then added slowly (24 h, 25 °C). The NMR spectra showed the formation of the new compound 19, containing the cyclopentyl ring, which was isolated in excellent yield (92%). The deprotection of the side chain was done using the classical reaction conditions, and compound **21**,¹² in which the aldehyde function is protected as its dimethyl acetal, was isolated in 70% yield (mixture of diastereomers, 77:10:8:5). The reaction is diastereoselective giving compound **21** as the main isomer, characterized by a cis relationship between the two carbon residues which are trans oriented with respect to the hydroxy groups on the ring (see the Supporting Information). These results show that the C-13 chain does not influence the stereochemical result of the above reaction since the stereochemistry of the main epimer and the distribution of the isomers was quite similar to that observed starting from 7b. This data confirms also that the water elimination can be ascribed to the action of DCC.

The purification of the mixture of isomers by semipreparative HPLC allowed isolation of the main isomer in pure form, indicating that it is more stable with respect to derivatives 8 containing the unprotected aldehyde.

The formyl group in compound **19** was also reduced to the corresponding alcohol **20** (50%) performing the reaction in EtOH at -20 °C in the presence of NaBH₄ (1 h).

Operating as described above, the oxygen and nitrogen atoms of the chain of **20** were deprotected giving compound **22**.¹² Only trace amounts of a second diastereomer were detected in the NMR spectra. Interestingly, the transposition of the acyl group from C-20 to the CH₂OH group was observed, as well as the formation of an ortho ester generated by reaction of the hydroxy group at C-20 with the carbonyl function of the benzoate at C-2, thus confirming the stereochemistry assigned to the C-4 stereocenter (see the Supporting Information for details).

On the basis of the above synthetic results, we can conclude that both the condensation reaction giving the tetrahydrofuranosyl ring and the cyclopentyl ring, respectively, occur with good diastereoselectivity and that the configuration at the C-4

SCHEME 5. Stereochemistry in the Formation of the C-Ring



stereocenter is the same in all cases. This means that the keto function in the chain linked at C-3 on compounds **7** is typically β -oriented (Scheme 5) and that the intramolecular attack of the nucleophile (i.e., the hydroxy group to give compound **6** or the carbon in the formation of compounds **8**) generates a new stereocenter in which the hydroxy group is in the β -position. The same is also true for the transformation of **18** into **19**.

Concerning the stereochemical result observed in the formation of the new stereocenter α to the aldehyde group on the cyclopentane ring, a reasonable hypothesis is that the more stable *E* enolate was first formed (intermediate **A**) by deprotonation of the carbon α to the aldehyde function promoted by pyridine. A pyridinium ion is formed which protonates the enolate giving enol **B**, whose conformation is stabilized by formation of a hydrogen bond between the hydroxy group and the keto function on the C-3 chain, thus increasing the electrophilicity of the latter group. Alternatively, **B** could be formed directly when Py•HF is used. The hypothesis that **B** is the true intermediate is confirmed by the fact that Py•HF is a more effective catalyst. Indeed, the aldol condensation performed in the presence of Py•HF takes place in 1 day (compounds 8a and 19), whereas when pyridine alone is used the reaction needs 3 days (compound 8b). As a result of the formation of intermediate B, a cyclopentane ring is formed in which the hydroxy groups are oriented cis to each other and trans with respect to the carbon residues.

The biological activity of compounds **12**, **13**, **16**, **17**, **21**, and **22** was evaluated and compared to paclitaxel. No significant cytotoxic activity on the lung carcinoma cell line H460 (see the Supporting Information, TS1) was evidenced except for compound **21**, which still retained a measurable activity but was characterized by a markedly lower potency.

Aiming to verify if the low activity could be ascribed to the difficulty in cell penetration, the same compounds were evaluated in a tubulin-assembly assay using bovine pure tubulin. The results, summarized in TS1 (Supporting Information), show that all compounds are unactive compared to paclitaxel.

These results indicate that changes in the size and conformation of ring C and the absence of D ring make a significant difference in the activity of paclitaxel, confirming the general trends observed for other C-nor and C-nor-D-seco-taxane derivatives.^{9b,c}

In conclusion, the preparation of new D-seco-C-nor-taxane derivatives containing the polyfunctionalized tetrahydrofuranosyl or cyclopentenyl or cyclopentyl C-ring was performed starting from the readily available baccatin derivatives **3**. The kind of ring formed is strictly dependent on the presence of an unprotected or protected oxygen at C-7 on the starting material. In all cases, the β -stereochemistry of the C-4 hydroxy group

was obtained. Concerning the cyclopentyl derivatives, the presence or absence of DCC controls the reaction toward the formation of the cyclopentenyl or cyclopentyl ring, respectively. In all cases, the condensation reaction proceeds with good diastereoselectivity, and compounds characterized by having the two hydroxy groups cis oriented to each other and trans with respect to the carbon residues on the C-ring were obtained.

Experimental Section

General Procedure for the Oxidation of the C-Ring. Compound 4a (100 mg, 0.165 mmol) or 4b (500 mg, 0.70 mmol) was dissolved in dry CH₂Cl₂ (4a: 1.6 mL, 4b: 10 mL). A fresh batch of lead tetraacetate (4a: 80.6 mg, 0.182 mmol; 4b: 677.8 mg, 1.53 mmol) was added to the solution cooled at 0 °C. After 30 min, the solvent was removed in vacuo, and the residue was directly purified by column chromatography (silica gel, EtOAc/cyclohexane = 1:1) affording the C,D-seco compound 6 (84 mg, 84%; TLC: $R_f = 0.4$ (CH₂Cl₂/MeOH = 10:1) from 4a and compound 7b (490 mg, 95% $R_f = 0.58$, CH₂Cl₂/MeOH 10:1) from 4b.

C-nor-D-seco-Baccatin III Derivative 6: mp 235 °C dec (Et₂O/ *n*-pentane); white solid; $[\alpha]^{20}_{D}$ -42 (*c* 0.16, CHCl₃); IR ν_{max} 3600-3400, 1736, 1702, 1687 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.10 (s, 3H), 1.13 (s, 3H), 1.60-1.80 (m, 2H, exch.), 2.04 (s, 3H), 2.14 (s, 3H), 2.20 (s, 3H), 2.24 (s, 3H), 2.58 (s, 1H, exch.), 2.43-2.60 (m, 4H), 3.71 (d, J = 8.7 Hz, 1H), 3.92, 4.39 (AM system J = 11.6 Hz, 2H), 4.64 (dd, J = 2.4, 11.5 Hz, 1H), 4.86 (t, J = 7.2 Hz, 1H), 5.79 (d, J = 8.7 Hz, 1H), 6.24 (s, 1H), 7.46-7.73 (m, 3H), 8.00-8.15 (m, 2H), 9.59 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 15.2, 19.3, 20.0, 20.4, 22.4, 26.3, 40.7, 41.0, 45.3, 46.3, 59.7, 65.9, 67.0, 73.5, 76.3, 78.0, 82.5, 105.2, 128.0 (× 2C), 128.9 (× 2C), 129.2, 132.6, 133.2, 143.2, 165.6, 169.2, 169.9, 197.3, 202.9; MS (ESI) *m*/z 625.4 [M + 23]⁺. Anal. Calcd for C₃₁H₃₈O₁₂: C, 61.78; H, 6.36. Found: C, 61.70; H, 6.42.

C,D-seco-Baccatin III Derivative 7b: mp 122 °C (Et₂O/npentane); white solid; $[\alpha]^{20}_{D}$ -62 (c 0.20, CHCl₃); IR ν_{max} $3700-3150, 1732 \text{ cm}^{-1}$; ¹H NMR (200 MHz, CDCl₃) δ 0.57-0.78 (m, 6H), 0.95 (t, J = 7.9 Hz, 9H), 1.05 (s, 3H), 1.15 (s, 3H), 1.52 (s, 3H), 1.97 (s, 3H), 2.10 (s, 3H), 2.24 (s, 3H), 1.80-2.40 (m, 2H, exch.), 2.52–2.58 (m, 2H), 2.62 (dd, J = 4.4, 15.8 Hz, 1H), 2.80 (dd, J = 4.8, 18.7 Hz, 1H), 4.44 (t, J = 4.8 Hz, 1H), 4.75 (d, J = 7.3 Hz, 1H), 4.82, 5.32 (AM system, J = 17.4 Hz, 2H), 4.85-4.90 (m, 1H), 5.80 (d, J = 7.3 Hz, 1H), 6.25 (s, 1H), 7.41-7.47 (m, 2H), 7.58-7.61 (m, 1H), 7.97-8.0 (m, 2H), 9.70 (s, 1H); ¹³C NMR (50 MHz, CDCl₃) δ 4.5 (× 3C), 6.2 (× 3C), 16.1, 16.4, 19.2, 19.6, 20.2, 27.4, 38.5, 41.4, 47.6, 49.4, 59.2, 67.2, 69.3, 71.6, 73.7, 77.2, 78.9, 127.6 (× 2C), 127.8, 128.4 (× 2C), 129.3, 132.7, 133.0, 142.7, 165.2, 169.0, 198.5, 199.2, 204.3. MS (ESI) m/z 739.5 [M + 23]⁺. Anal. Calcd for C₃₇H₅₂O₁₂Si: C, 61.99; H, 7.31. Found: C, 61.93; H, 7.29.

C-nor-D-seco-Baccatin III Derivatives 8 (Method A). A solution of 7b (360 mg, 0.49 mmol) in MeCN (17 mL) and pyridine (17 mL) was cooled to 0 °C, and a solution of HF • Py (3.17 mL) was slowly added. The reaction mixture was stirred for 24 h at 25 °C and then quenched with ice and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with NaHSO₄ (2 M) to pH 2, then with aqueous NaHCO₃ (5%, 40 mL), and finally with brine (40 mL). After drying over Na₂SO₄ and evaporation, the crude reaction mixture was purified by silica gel chromatography (EtOAc/ cyclohexane = 2:3; TLC: $R_f = 0.11$, CH₂Cl₂/MeOH, 10:1) affording 8a (260 mg, 88%) as a mixture of isomers (80:10:7:3 ratio, ¹H NMR analysis). A partial purification of the mixture using semipreparative HPLC (reversed-phase column, 150 Å, 5 μ m, 250 mm \times 10 mm, H₂O/MeCN 52:48, 1 mL/min) is possible. (Method B) A mixture of 7b (25 mg, 0.03 mmol) in MeCN (1 mL) and pyridine (0.3 mL) was stirred for 3 days at 25 °C. The reaction mixture was elaborated as described for **7a**. Compound **8b** (21 mg, 98%; $R_f =$ 0.5, CH₂Cl₂/MeOH, 10:1) was obtained as a mixture of epimers (77:11:8:4 ratio, ¹H NMR analysis). Attempts to purify the mixture using semipreparative HPLC (reversed-phase column, 150 Å, 5 μ m, 250 mm × 10 mm, H₂O/MeCN 30:70, 1 mL/min) failed.

8a: mp 122–125 °C (Et₂O/*n*-pentane); $[\alpha]^{20}_{D}$ –47 (*c* 0.30, CHCl₃); IR v_{max} 3700–3150, 1725 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.10 (s, 3H), 1.13 (s, 3H), 1.23–1.27 (m, 2H, exch.), 1.67 (s, 3H), 2.03 (s, 3H), 2.07 (s, 3H), 2.23 (s, 3H), 2.42-2.48 (m, 2H), 2.54 (brs, 1H, exch), 2.97 (d, J = 9.5 Hz, 1H), 3.18–3.21 (m, 1H, exch.), 3.27 (d, J = 8.3 Hz, 1H), 4.19, 4.46 (AM system, J = 11.5 Hz, 2H), 4.29 (d, J = 9.5 Hz, 1H), 4.82 (t, J = 7.3, 1H), 5.84 (d, J = 8.3 Hz, 1H), 6.48 (s, 1H), 7.47 (t, J = 7.70 Hz, 2H), 7.59 (t, J = 7.33 Hz, 1H), 8.04 (d, J = 6.9 Hz, 2H), 9.85 (s, 1H); main signals for other isomers: δ H-2 5.88 (d, J = 8.0 Hz), 5.95 (d), 5.62 (d); H-10 6.58 (s), 6.55 (s), 6.42 (s); CHO 9.98 (s), 9.83 (s), 9.77 (s); ¹³C NMR (125 MHz, CDCl₃) δ 12.2, 14.9, 19.3, 20.1, 20.2, 26.5, 39.3, 41.1, 47.3, 60.1, 66.0, 66.2, 66.7, 73.4, 73.8, 74.5, 77.9, 80.3, 128.1 (× 2C), 128.9, 129.1 (× 2C), 132.8, 133.2, 142.6, 165.9, 169.5, 169.6, 199.4, 203.8; MS (ESI) *m*/*z* 625.4 [M + 23]⁺. Anal. Calcd for C₃₁H₃₈O₁₂: C, 61.78; H, 6.36. Found: C, 61.70; H, 6.40.

8b: mp 128–131 °C (Et₂O/*n*-pentane); $[\alpha]^{20}_{D}$ –53 (*c* 0.20, CHCl₃); IR ν_{max} 3700–3150, 1725 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.34 (q, J = 7.9 Hz, 6H), 0.93 (t, J = 7.9 Hz, 9H), 1.10 (s, 3H), 1.15 (s, 3H), 1.28 (s, 2H, exch.), 1.66 (s, 3H), 2.03 (s, 3H), 2.16 (s, 3H), 2.24 (s, 3H), 2.32-2.38 (m, 1H, exch.), 2.40-2.50 (m, 2H), 3.05 (dd, J = 8.5, 2.0 Hz, 1H), 3.26 (d, J =8.1 Hz, 1H), 4.02, 4.67 (AM system, J = 11.7 Hz, 2H), 4.38 (d, J = 8.5 Hz, 1H), 4.80 (t, J = 6.0 Hz, 1H), 5.84 (d, J = 8.1 Hz, 1H), 6.55 (s, 1H), 7.47–8.07 (m, 5H), 9.94 (d, J = 2.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 4.0 (× 3C), 6.0 (× 3C), 12.2, 14.7, 19.0, 20.1 (× 2C), 26.5, 39.0, 41.2, 47.6, 61.3, 66.8, 66.9, 68.4, 73.4, 74.3, 74.6, 77.7, 81.1, 128.0 (× 2C), 128.8, 129.2 (× 2C), 132.8, 133.7, 141.5, 165.9, 168.6, 169.5, 199.7, 202.1; main signals for other epimers: ¹H NMR δ H-6 2.96 (dd, J = 9.8, 2.8 Hz); H-2 5.90 (d, J = 8.1 Hz), 5.62 (d, J = 8.6 Hz), 5.75; H-10 6.50 (s), 6.62 (s); CHO 9.75 (d, J = 2.9 Hz), 9.64 (d), 9.82 (d); MS (ESI) m/z 739.2 [M + 23]⁺. Anal. Calcd for C₃₇H₅₂O₁₂Si: C, 61.99; H, 7.31. Found: C, 61.92; H, 7.36.

Synthesis of Compound 12. Compound 10 (415 mg, 96%) was obtained from compound 6 (300 mg, 0.49 mmol) and free acid 9 (330 mg, 0.8 mmol) operating as decribed in the Supporting Information. Column chromatography: EtOAc/cyclohexane (from 1:9 to 1:4; TLC: $R_f = 0.73$, CH₂Cl₂/MeOH = 10:1). Compound 12 (88 mg, 40%; mixture of isomers, 87:13) was isolated after deprotection of the chain (see the Supporting Information) starting from 10 (263 mg, 0.26 mmol). Column chromatography: EtOAc/ cyclohexane (from 1:3 to 1:2; TLC: $R_f = 0.6$, $CH_2Cl_2/MeOH =$ 10:1). Attempts to purify the mixture using semipreparative HPLC (reversed-phase column, 150 Å, 5 μ m, 250 mm \times 10 mm, H₂O/ MeCN 40:60, 1 mL/min) failed: mp 158-160 °C (Et₂O/n-pentane); $[\alpha]^{20}_{D}$ -40 (c 0.16, CHCl₃); IR ν_{max} 3450, 1740, 1712 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.98-1.01 (m, 6H), 1.19 (s, 3H), 1.23 (s, 3H), 1.36 (s, 9H), 1.38-1.40 (m, 1H), 1.65-1.78 (m, 2H + 2H exch.), 2.00 (s, 3H), 2.03 (s, 3H), 2.11 (s, 3H), 2.25 (s, 3H), 2.42-2.55 (m, 3H), 2.65 (s, 1H, exch.), 2.81 (dd, J = 16.1, 6.1Hz, 1H), 3.72 (d, J = 8.2 Hz, 1H), 4.18-4.30 (m, 2H), 4.35 (brs, 2H), 4.65 (t, J = 6.8 Hz, 1H), 4.71 (d, J = 9.4 Hz, 1H, exch.), 5.84 (d, J = 8.2 Hz, 1H), 6.16-6.22 (m, 1H), 6.24 (s, 1H), 7.40–8.20 (m, 5H), 9.60 (s, 1H); 13 C NMR (125 MHz, CDCl₃) δ 15.1 (14.9), 19.1, 20.0, 20.2, 20.8 (× 2C), 22.6, 24.1, 26.3, 27.6 (× 3C), 35.7 (35.5), 40.6, 41.2, 46.3, 46.7, 50.5, 59.5, 66.9, 70.8, 72.5, 72.8, 76.3, 77.1, 78.7, 82.5 (84.6), 104.7, 128.0 (× 2C), 128.9, 129.2 (× 2C), 132.4, 135.7, 138.7 (138.4), 154.6, 165.7, 169.1, 169.3, 172.6, 197.2, 202.8 (202.5); significant signals for the isomer: ¹H NMR δ 4.49 (d, J = 8.6 Hz, 1H), 6.32 (s, 1H); MS (ESI) m/z868.6 [M + 23]⁺. Anal. Calcd for C₄₃H₅₉NO₁₆: C, 61.05; H, 7.03; N, 1.66. Found: C, 60.95; H, 7.11; N, 1.62.

Synthesis of Compound 13. Compound **11** (205 mg, 45%) was obtained after reduction with NaBH₄ (4.86 mg, 0.128 mmol) of **10**

(400 mg, 0.457 mmol) operating as decribed in the Supporting Information. Column chromatography: EtOAc/cyclohexane (from 9:1 to 2:1; TLC: $R_f = 0.28$, $CH_2Cl_2/MeOH = 10:1$). The deprotection of the chain on compound 11 (138 mg, 0.157 mmol) was performed as reported in the Supporting Information, and 13 (84 mg, 63%) was isolated in pure form. Column chromatography: EtOAc/cyclohexane (from 1:3 to 3:5; TLC: $R_f = 0.44$, $CH_2Cl_2/$ MeOH = 10:1): mp 150 °C (Et₂O/*n*-pentane); $[\alpha]^{20}_{D}$ -19 (*c* 0.14, CHCl₃); IR ν_{max} 3500–3400, 1736, 1712 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) & 0.97-1.10 (m, 6H), 1.19 (s, 3H), 1.22 (s, 3H), 1.34-1.38 (m, 10H), 1.45 (s, 3H), 1.57-1.77 (m, 4H), 1.94-1.98 (m, 2H, exch.), 1.99 (s, 3H), 2.09 (s, 3H), 2.25 (s, 3H), 2.49 (dd, J = 16.0, 10.2 Hz, 1H), 2.77 (s, 1H, exch.), 2.83 (dd, J = 16.0, 5.6Hz, 1H), 3.20-3.32 (s, 1H, exch.), 3.69-3.77 (m, 3H), 4.22 (dd, J = 11.2, 2.3 Hz, 1H), 4.23-4.28 (m, 2H) 4.36, 4.48 (AB system, J = 11.3 Hz, 2H), 4.71 (d, J = 9.8 Hz, 1H, exch), 5.84 (d, J = 8.5Hz, 1H), 6.16-6.21 (m, 1H), 6.31 (s, 1H), 7.44-8.22 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 15.9, 19.7, 20.7, 20.9, 21.5, 23.2, 23.3, 24.8, 27.1, 28.3 (× 3C), 35.6, 36.3, 41.3, 41.9, 47.6, 51.1, 60.7, 60.8, 68.3, 71.6, 73.2, 73.6, 77.0, 77.8, 79.4, 88.1, 105.1, 128.6 (× 2C), 130.0 (× 2C), 131.0, 133.1, 136.5, 139.0, 155.2, 166.5, 169.8, 170.3, 173.3, 203.6. MS (ESI) m/z 870.5 [M + 23]⁺. Anal. Calcd for C₄₃H₆₁NO₁₆: C, 60.91; H, 7.25; N, 1.65. Found: C, 60.85; H, 7.29; N, 1.62.

Synthesis of Compound 16. Operating as decribed in the Supporting Information, compound 14 (432 mg, 61%, mixture of isomers) was obtained from compound 8a (260 mg, 0.432 mmol) and 9 (295.2 mg, 0.726 mmol). Column chromatography: EtOAc/ cyclohexane (from 1:9 to 1:4; $R_f = 0.61$, CH₂Cl₂/MeOH, 10:1). The deprotection of the side chain in 14 (150 mg, 0.151 mmol) was performed as described in the Supporting Information, and compound 16 (49 mg, 37%; mixture of isomers, 83:17) was obtained after column chromatography: EtOAc/cyclohexane (from 1:5 to 1:1; $R_f = 0.37$, cyclohexane/AcOEt, 1:1). Attempts to purify the mixture using semipreparative HPLC (reversed-phase column, 150 Å, 5 μ m, 250 mm × 10 mm, H₂O/MeCN 30:70, 1 mL/min) failed: mp 117-121 °C (Et₂O/*n*-pentane); [α]²⁰_D -115 (*c* 0.200, CHCl₃); IR ν_{max} 3700–3150, 1737, 1713 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.02 (d, J = 6.6 Hz, 6H), 1.22 (s, 3H), 1.28 (s, 3H), 1.36 (s, 9H), 1.45-1.80 (m, 4H), 1.82 (s, 3H), 1.89 (s, 3H), 2.10 (s, 3H), 2.24 (s, 3H), 2.55 (dd, *J* = 16.1, 9.9 Hz, 1H), 2.64 (s, 1H, exch.), 2.73 (dd, J = 16.1, 7.3 Hz, 1H), 3.27 (s, 3H), 3.33 (s, 3H), 3.35-3.40 (m, 1H, exch.), 3.64 (d, J = 8.1, 1H), 4.17-4.25(m, 2H), 4.41, 4.45 (AB system, J = 11.3 Hz, 2H), 4.68 (d, J =9.7 Hz, 1H, exch.), 4.78 (s, 1H), 5.86 (d, J = 8.01 Hz, 1H), 5.92 (s, 1H), 6.18-6.21 (m, 1H), 6.24 (s, 1H), 7.42-7.50 (m, 2H), 7.55-7.60 (m, 1H), 8.15-8.20 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) & 15.2, 20.3, 20.74, 21.32, 21.5, 23.4, 24.0, 24.8, 26.6, 28.2 (× 3C), 37.1, 41.1, 42.3, 47.8, 51.4, 54.0 (× 2C), 62.6, 66.5, 71.8, 73.2, 75.2, 75.6, 77.8, 79.4, 83.7, 101.2, 128.6 (× 2C), 130.0 (× 2C), 130.4, 133.1, 136.3, 139.9, 140.5, 145.2, 155.3, 166.4 (× 2C), 169.7, 173.5, 203.5; significant signals for isomer: ¹H NMR δ 1.06 (d, J = 6.4 Hz, 6H), 1.25 (s, 3H), 1.86 (s, 3H), 2.26 (s, 3H), 3.71 (d, J = 8.3 Hz, 1H), 4.11-4.14 (m, 2H), 4.63 (d, J = 9.7 Hz, 1H, exch.), 6.74 (s, 1H); ¹³C NMR δ 20.75, 21.33, 21.6, 24.6, 26.8, 37.3, 47.6, 51.0, 54.1, 54.0, 62.0, 66.9, 71.9, 75.8, 77.9, 83.9, 128.5, 132.8, 136.7, 139.3, 157.7, 169.6, 173.4, 205.0; MS (ESI) m/z 896.4 $[M + 23]^+$. Anal. Calcd for C₄₅H₆₃NO₁₆: C, 61.84; H, 7.27; N, 1.60. Found: C, 61.79; H, 7.30; N, 1.57.

Synthesis of Compound 17. The reduction with NaBH₄ (1.2 mg, 0.032 mmol) of the formyl group on 14 (110 mg, 0.111 mmol) was performed as reported in the Supporting Information, and compound 15 (54 mg, 50%) was isolated after column chromatography (EtOAc/cyclohexane = 1:4; $R_f = 0.64$, CH₂Cl₂/MeOH, 9:1). The deprotection of the side chain in compound 15 (55 mg, 0.055 mmol) was performed as reported in the Supporting Information. Compound 17 (41 mg, 90%; mixture of isomers, 89:11) was purified by column chromatography (EtOAc/cyclohexane, from 1:3 to 1:1; $R_f = 0.39$, CH₂Cl₂/MeOH, 9:1). It is possible to isolate pure

17 by semipreparative HPLC (reversed-phase column, 150 Å, 5 μ m, 250 mm × 10 mm, H₂O/MeCN 40:60, 1 mL/min). Pure isomer: mp 127–130 °C (Et₂O/*n*-pentane); $[\alpha]^{20}_{D}$ –58 (*c* 0.30, CHCl₃); IR ν_{max} 3700–3150, 1713 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.02 (d, J = 6.6 Hz, 3H), 1.05 (d, J = 5.4 Hz, 3H), 1.21 (s, 3H),1.24 (s, 3H), 1.37 (s, 9H), 1.40-1.70 (m, 5H), 1.81 (s, 3H), 1.86 (s, 3H), 2.10 (s, 3H), 2.24 (s, 3H), 2.52 (s, 1H, exch.), 2.56 (dd, J = 16.0, 9.5 Hz, 1H), 2.72 (dd, J = 16.0, 7.1 Hz, 1H), 3.40 (s, 1H, exch.), 3.64 (d, J = 7.9 Hz, 1H), 4.10–4.30 (m, 4H), 4.39, 4.64 (AB system, J = 11.6 Hz, 2H), 4.71 (d, J = 9.4 Hz, 1H, exch.), 5.76 (s, 1H), 5.85 (d, J = 7.9 Hz, 1H), 6.17–6.20 (m, 1H), 6.21 (s, 1H), 7.40–8.19 (m, 5H); 13 C NMR (125 MHz, CDCl₃) δ 15.3, 20.2, 20.8, 21.2, 21.6, 23.3, 24.5, 24.8, 26.9, 28.3 (× 3C), 37.2, 41.0, 42.4, 47.9, 51.4, 59.8, 61.6, 67.4, 71.8, 73.2, 75.3, 75.8, 77.9, 79.4, 84.4, 128.5 (× 2C), 130.0 (× 2C), 130.3, 133.0, 137.0, 138.8, 139.2, 144.1, 155.3, 166.5, 170.0, 170.4, 173.4, 204.9; MS (ESI) m/z 852.7 [M + 23]⁺. Anal. Calcd. for C₄₃H₅₉NO₁₅: C, 62.23; H, 7.17; N, 1.69. Found: C, 62.20; H, 7.13; N, 1.67.

Synthesis of Compound 19. Compound 18 (128 mg, 75%, mixture of isomers) was prepared according to the general procedure (see the Supporting Information) from 7b (110 mg, 0.14 mmol) and 9 (101.7 mg, 0.25 mmol). Column chromatography: EtOAc/ cyclohexane (from 1:9 to 1:4; $R_f = 0.81$, CH₂Cl₂/MeOH, 10:1). A solution of 18 (610 mg, 0.533 mmol) in MeCN (18.6 mL) and pyridine (18.6 mL) was cooled to 0 °C for 10 min, after which a solution of HF+Py (3.57 mL) was slowly added. The reaction mixture was stirred for 24 h at room temperature, and then it was quenched with ice-water (57 mL) and extracted with CH₂Cl₂ $(3 \times 20 \text{ mL})$. The organic layer was washed with NaHSO₄ (2 M) to pH 2, then with NaHCO₃ (5%, 50 mL), and finally with brine (50 mL). After drying over Na₂SO₄ and evaporation of the solvent, the crude product was purified by silica gel column chromatography (EtOAc/cyclohexane = 1:1; $R_f = 0.33$, CH₂Cl₂/MeOH, 10:1) to give **19** (mixture of isomers, 489 mg, 92%): IR ν_{max} 3700–3150, 1740, 1708 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ1.05-1.55 (m, 22H), 1.60-1.90 (m, 2H), 1.67 (s, 3H), 1.94 (s, 3H), 2.09 (s, 3H), 2.26 (s, 3H), 2.37 (dd, J = 15.3, 5.3 Hz, 1H), 2.47–2.53 (m, 1H, exch.), 2.59 (dd, J = 15.3, 9.6 Hz, 1H), 2.96 (d, J = 9.6 Hz, 1H), 3.10-3.15 (m, 1H, exch.), 3.17 (d, J = 8.2 Hz, 1H), 3.40-3.48(m, 1H), 3.84 (s, 6H), 3.92 (d, J = 13.3 Hz, 1H), 4.25 (d, J = 9.6 Hz, 1H), 4.40-4.65 (m, 3H), 5.88 (d, J = 8.2 Hz, 1H), 6.00-6.09(m, 1H), 6.40-6.60 (m, 4H), 7.20-7.28 (m, 1H), 7.45-7.55 (t, J = 7.9 Hz, 2H), 7.55-7.65 (m, 1H), 7.98-8.10 (m, 2H), 9.80 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 12.9, 15.2, 20.2, 20.6, 20.8, 21.8, 22.2, 23.1 (23.3), 28.2 (× 3C), 36.8, 42.1, 43.2, 48.0, 49.4, 55.4 (× 2C), 57.9, 58.7, 60.8, 66.7, 66.8, 70.8, 73.4, 74.5, 74.9, 77.3, 78.5, 80.6, 86.0, 98.4, 104.4 (104.3), 117.9, 128.7, 128.9 (× 2C), 129.4, 129.8 (× 2C), 133.6, 135.8, 139.5, 153.4, 159.0, 161.5, 166.5, 169.8 (× 2C), 170.4, 199.4, 204.1; MS (ESI) m/z 1016.5 [M + 23]⁺. Anal. Calcd for C₅₂H₆₇NO₁₈: C, 62.83; H, 6.79; N, 1.41. Found: C, 62.76; H, 6.84; N, 1.37.

Synthesis of Compound 21. Deprotection of the side chain in compound 19 (200 mg, 0.19 mmol) was performed as described in the Supporting Information, and compound 21 (121 mg, 70%; mixture of isomers, 77:10:8:5) was isolated after column chromatography (SiO₂: EtOAc/cyclohexane, from 1:3 to 3:5; $R_f = 0.43$, CH₂Cl₂/MeOH, 9:1). It is possible to isolate pure 21 by semipreparative HPLC (reversed-phase column, 150 Å, 5 μ m, 250 mm × 10 mm, H₂O/MeCN 40:60, 1 mL/min). Pure isomer: mp 145–147 °C (Et₂O/*n*-pentane); $[\alpha]^{20}_{D}$ –52 (*c* 0.30, CHCl₃); IR ν_{max} 3700-3150, 1737, 1713 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.98-1.05 (m, 6H), 1.17 (s, 3H), 1.18 (s, 3H), 1.40 (s, 9H), 1.45-1.80 (m, 3H + 2H exch.), 1.68 (s, 3H), 1.95 (s, 3H), 2.06 (s, 3H), 2.24 (s, 3H), 2.31 (dd, J = 9.0, 3.8 Hz, 1H), 2.55-2.60 (m, 2H), 2.70 (s, 1H exch.), 3.08 (d, J = 7.9 Hz, 1H), 3.40 (s, 3H), 3.44 (s, 3H), 3.71 (d, J = 5.8 Hz, 1H, exch), 4.15–4.24 (m, 2H), 4.34-4.37 (m, 1H), 4.39, 4.68 (AB system, J = 11.2 Hz, 2H), 4.62 (d, J = 3.8 Hz, 1H), 4.81 (d, J = 9.7 Hz, 1H, exch.), 5.86 (d, J = 7.9 Hz, 1H), 6.02–6.08 (m, 1H), 6.52 (s, 1H), 7.42–8.10 (m,

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5H); ¹³C (125 MHz, CDCl₃) δ 11.8, 14.5, 19.2, 20.1, 20.3, 21.2, 22.5, 24.1, 26.3, 27.6 (× 3C), 35.7, 40.1, 41.4, 47.8, 50.9, 55.2, 55.4, 57.8, 60.0, 67.4, 70.6, 72.5, 72.9, 73.5, 73.9, 77.2, 78.7, 78.9, 104.5, 127.8 (× 2C), 129.1, 129.2 (× 2C), 132.5, 135.6, 138.1, 154.7, 165.6, 168.9, 169.9, 172.5, 202.8; MS (ESI) *m/z* 914.5 [M + 23]⁺. Anal. Calcd for C₄₅H₆₅NO₁₇: C, 60.59; H, 7.34; N, 1.57. Found: C, 60.55; H, 7.38; N, 1.52.

Synthesis of Compound 22. Compound 20 (152 mg, 50%, mixture of isomers) was obtained after reduction of 19 (300 mg, 0.302 mmol) with NaBH₄ (3.21 mg, 0.0845 mmol) according to the general procedure (see the Supporting Information). Column chromatography: EtOAc/cyclohexane (1:4; $R_f = 0.39$, CH₂Cl₂/ MeOH, 9:1). The deprotection of the side chain in compound 20 (140 mg, 0.141 mmol) was performed as described in the Supporting Information to give pure 22 (46 mg, 38.5%). Column chromatography: EtOAc/cyclohexane (1:3; $R_f = 0.42$, CH₂Cl₂/ MeOH, 10:1): mp 143 °C (Et₂O/*n*-pentane); $[\alpha]^{20}_{D}$ -9 (*c* 0.3, CHCl₃); IR ν_{max} 377–3150, 1740 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) & 0.95-1.00 (m, 6H), 1.15 (s, 3H), 1.23 (s, 3H), 1.29 (m, 1H, exch.), 1.39 (s, 9H), 1.54 (s, 3H), 1.48-1.72 (m, 3H), 1.78 (s, 1H, exch.), 1.92 (s, 3H), 2.12 (s, 3H), 2.24 (s, 3H), 2.58-2.69 (m, 3H), 2.85 (m, 1H, exch.), 2.94 (m, 1H, exch.), 3.28 (d, J = 7.4 Hz, 1H), 3.83 (d, J = 7.8 Hz, 1H), 3.87–3.94 (m, 2H), 3.96 (d, J =10.5 Hz, 1H), 4.18–4.24 (m, 3H), 4.29 (dd, *J* = 12.2, 2.3 Hz, 1H), 4.37 (dd, J = 12.2, 3.4 Hz, 1H), 5.01 (d, J = 8.1 Hz, 1H, exch.), 6.00–6.07 (m, 1H), 6.38 (s, 1H), 7.37–7.43 (m, 3H), 7.60–7.65 (m, 2H); 13 C NMR (125 MHz, CDCl₃) δ 12.4, 14.7, 19.3, 20.1 (× 2C), 21.4, 22.0, 24.2, 26.0, 27.5 (× 3C), 35.6, 39.0, 40.8, 46.2, 47.9, 51.7, 58.6, 59.7, 71.2, 71.3, 73.0, 73.1, 73.6, 74.8, 75.8, 79.4, 82.1, 116.8, 125.4 (× 2C), 127.4 (× 2C), 129.0, 135.4, 137.0, 138.4, 155.6, 169.3 (× 2C), 172.0, 204.7; MS (ESI) *m*/*z* 870.2 [M + 23]⁺. Anal. Calcd. for C₄₃H₆₁NO₁₆: C, 60.91; H, 7.25; N, 1.65. Found: C, 60.89; H, 7.27; N, 1.63.

Supporting Information Available: Experimental details: general procedure; synthesis of 4a,b, 5a,b, and 9; general procedure for the coupling of 9 with derivatives 6, 8a, and 7b; general procedure for the reduction of the formyl group; general procedure for the deprotection of the chain. ¹H and ¹³C NMR data for compounds 4a,b, 5a,b, 10, 11, 14, 15, 18, 20; spectroscopic discussion for compounds 4b, 5b, 6, 7b, 8a,b, 12, 13, 16, 17, and 21; ¹H and ¹³C NMR spectra for compounds 4a,b, 5a,b, 6, 7b, 8a,b, and 10–22; HPLC data for compounds 4a,b, 12, 16, 17, and 21 and biological activity for compounds 12, 13, 16, 17, 21, and 22. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801458J