JOC Article

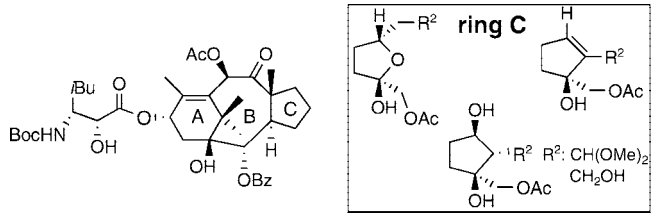
Semisynthesis of New D-seco-C-nor-Taxane Derivatives Containing a Polyfunctionalized Furanosyl or Cyclopentenyl or Cyclopentyl C-Ring

Maria Luisa Gelmi,*,† Donatella Nava,† Samantha Leone,† Sara Pellegrino,† Eleonora Baldelli,‡ Franco Zunino,§ Graziella Cappelletti,|| Daniele Cartelli,|| and Gabriele Fontana‡

Istituto di Chimica Organica "A. Marchesini" Facoltà di Farmacia, Università degli Studi di Milano, via Venezian 21, 20133, Milano, Italy, Indena SPA, via Ripamonti 99, 20141 Milano, Italy, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian 1, 20133 Milano, Italy, and Dipartimento di Biologia, Università degli Studi di Milano, Via Celoria, 26, 20133 Milano, Italy

marialuisa.gelmi@unimi.it

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

* To whom correspondence should be addressed. Phone: +390250314481. Fax: +390250314476.
† Istituto di Chimica Organica "A. Marchesini".
‡ Indena SPA.
§ Fondazione IRCCS.
|| Dipartimento di Biologia.

(1) (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.

10.1021/jo801458j CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/22/2008

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 anti-metastatic 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 C_6-C_7 or C_7-C_8 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 C_4-C_5 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 cyclopentyl (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.

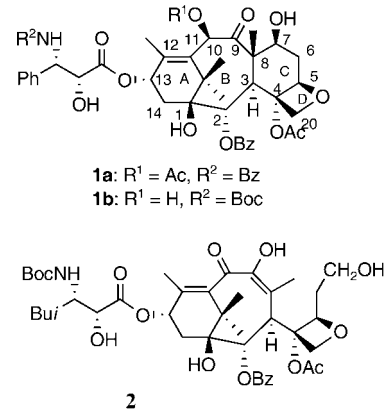


FIGURE 1. Taxane derivatives.

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 ($SnCl_4$) 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 $SnCl_4$ (1.1 equiv) in CH_2Cl_2 at 0 °C (10 min). TLC analysis showed the presence of two compounds (3:1, ^{1}H 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 $NaHCO_3$ (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 ^{1}H 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; Vo1. *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.; Glass, T.; Bane, S.; Ravindra, R.; Banerjee, A.; Metaferia, B.; Thomas, S. L.; Giannakakou, P.; Alcaraz, A. A.; Lakdawala, A. S.; Snyder, J. P.; Kingston, D. G. I. *J. Med. Chem.* **2007**, *50*, 713–725.

(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. 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.

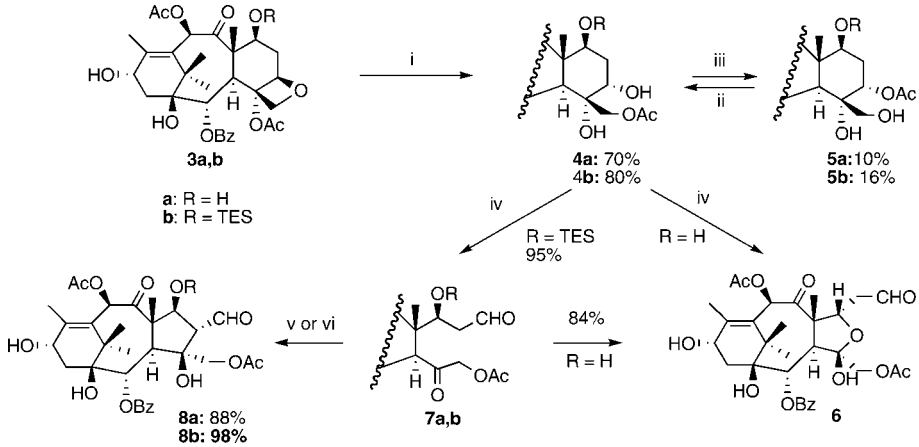
(6) (a) Fenoglio, I.; Nano, G. M.; Vander Velde, D. G.; Appendino, G. *Tetrahedron Lett.* **1996**, *37*, 3203–3206. (b) Marder-Karsenti, R.; Dubois, J.; Bricard, L.; Guénard, D.; Guéritte-Voegelein, F. *J. Org. Chem.* **1997**, *62*, 6631–6637. (c) Gunatilaka, A. A. L.; Ramdayal, F. D.; Sarragiotto, 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.

(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.; Dutta, 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.; Brinkhorst, 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.

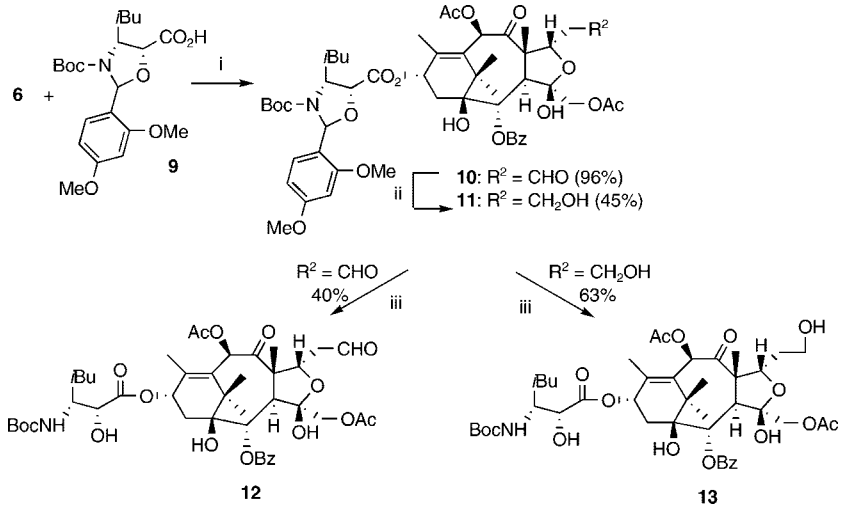
(9) (a) Magri, N. F.; Kingston, D. G. I. *J. Org. Chem.* **1986**, *51*, 797–802. (b) Liang, X.; Kingston, D. G. I. *Tetrahedron Lett.* **1995**, *36*, 7795–7798. (c) Liang, X.; Kingston, D. G. I.; Long, B. H.; Fairchild, C. A.; Johnston, K. A. *Tetrahedron* **1997**, *53*, 3441–3456. (d) Yuan, H.; Kingston, 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.

SCHEME 1. Synthesis of New D-seco-C-nor Derivatives 6 and 8[a]



[a] Reaction conditions: (i) $SnCl_4$, CH_2Cl_2, 0 °C; (ii) aqueous $NaHCO_3$ (5%, 0 °C); (iii) SiO_2; (iv) $Pb(OAc)_4$, CH_2Cl_2, 0 °C; (v) **8a**: MeCN/Py (1:1), Py·HF, 0 °C; (vi) **8b**: Py, 0 °C, MeCN.

SCHEME 2. Synthesis of D-seco-C-nor Derivatives 12 and 13 Containing a Tetrahydrofuranosyl C-Ring[a]



[a] Reaction conditions: (i) DMAP, DCC, CH_2Cl_2, 25 °C; (ii) $NaBH_4$, EtOH, −20 °C; (iii) CH_2Cl_2, 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 $NaHCO_3$ 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 ($NaIO_4$, HIO_4, $Pb(OAc)_4$). Lead tetraacetate was the most efficient reagent in CH_2Cl_2 at 0 °C (30 min), and the new derivative **6** (84%) was directly obtained from **4a** (Scheme 1). It is assumed that the C_4-C_5 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 literature[11] 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.

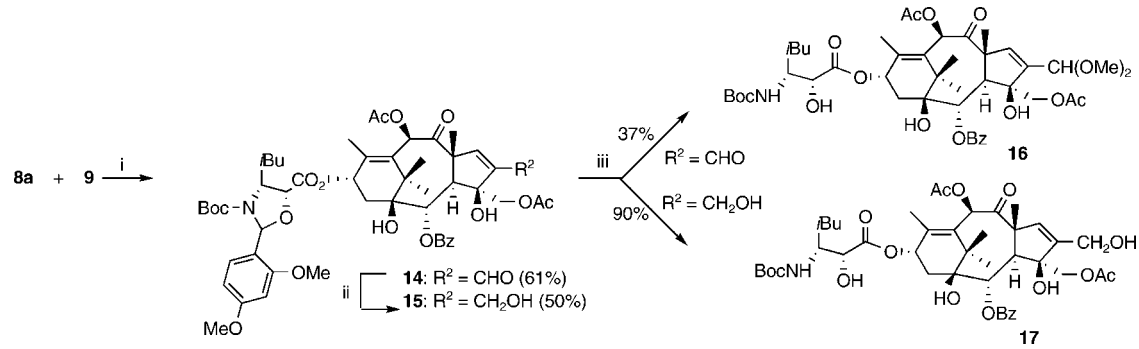
With the aim to isolate an intermediate structure **7**, the same oxidative protocol was applied to **4b**, which gave the expected C,D-seco compound **7b** in 95% yield.

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.

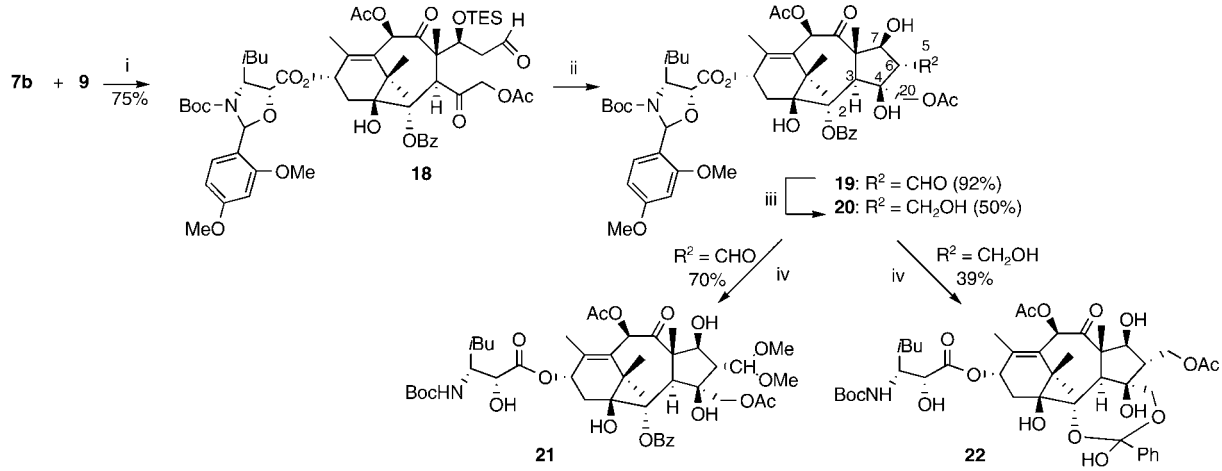
In principle, two different regioisomeric aldol products could be formed, the compounds deriving from the condensation of the carbon α to the keto group on the aldehyde function or that of the carbon α to the aldehyde group on the keto function. The presence of the aldehyde function (^1H and ^{13}C NMR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

SCHEME 3. Synthesis of D-seco-C-nor Derivatives 16 and 17 Containing a Cyclopentenyl C-Ring[a]



[a] Reaction conditions: (i) DMAP, DCC, CH_2Cl_2, 25 °C; (ii) $NaBH_4$, EtOH, −20 °C; (iii) CH_2Cl_2, 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, CH_2Cl_2, 25 °C; (ii) Py, MeCN, 0 °C, then Py·HF; (iii) $NaBH_4$, EtOH, −20 °C; (iv) CH_2Cl_2, 0 °C, 0.01 M AcCl in MeOH.

and a mixture of isomers (80:10:7:3; ^{1}H 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/H_2O, 1:1) resulted in an equilibration between the isomers due to a retro-condensation reaction operative in aqueous solution, even if the ^{1}H NMR spectrum in $CDCl_3$ of the main fraction showed only a trace amount of a second isomer (see HPLC and ^{1}H 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 then 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; ^{1}H 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 ^{1}H 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, CH_2Cl_2) 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 $NaBH_4$ 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.

(12) Only the main isomer has been drawn in Schemes 1−4.

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 $NaBH_4$ 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.

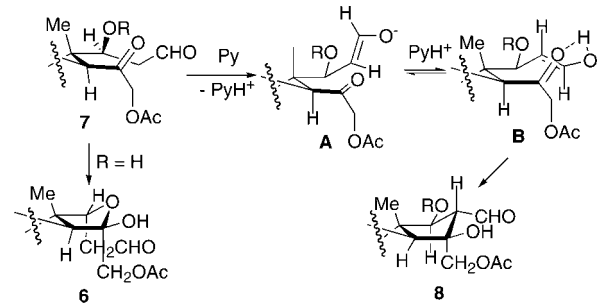
The purification of the mixture of isomers by semipreparative HPLC allowed isolation of the main isomer in pure form, indicating that it is more stable with respect to derivatives **8** containing the unprotected aldehyde.

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 $NaBH_4$ (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 CH_2OH 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 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**.

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



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 CH_2Cl_2 (**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: $R_f = 0.4$ (CH_2Cl_2/MeOH = 10:1) from **4a** and compound **7b** (490 mg, 95% $R_f = 0.58$, CH_2Cl_2/MeOH 10:1) from **4b**.

C-nor-D-seco-Baccatin III Derivative 6: mp 235 °C dec (Et_2O/*n*-pentane); white solid; $[\alpha]^{20}_D$ −42 (*c* 0.16, $CHCl_3$); IR ν_{max} 3600−3400, 1736, 1702, 1687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{31}H_{38}O_{12}$: C, 61.78; H, 6.36. Found: C, 61.70; H, 6.42.

C,D-seco-Baccatin III Derivative 7b: mp 122 °C (Et_2O/*n*-pentane); white solid; $[\alpha]^{20}_D$ −62 (*c* 0.20, $CHCl_3$); IR ν_{max} 3700−3150, 1732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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 $C_{37}H_{52}O_{12}Si$: 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 $NaHSO_4$ (2 M) to pH 2, then with aqueous $NaHCO_3$ (5%, 40 mL), and finally with brine (40 mL). After drying over Na_2SO_4 and evaporation, the crude reaction mixture was purified by silica gel chromatography (EtOAc/cyclohexane = 2:3; TLC: $R_f = 0.11$, CH_2Cl_2/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 μm, 250 mm × 10 mm, H_2O/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%; $R_f = 0.5$, CH_2Cl_2/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 μm, 250 mm × 10 mm, H_2O/MeCN 30:70, 1 mL/min) failed.

8a: mp 122−125 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −47 (*c* 0.30, $CHCl_3$); IR ν_{max} 3700−3150, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{31}H_{38}O_{12}$: C, 61.78; H, 6.36. Found: C, 61.70; H, 6.40.

8b: mp 128−131 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −53 (*c* 0.20, $CHCl_3$); IR ν_{max} 3700−3150, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{37}H_{52}O_{12}Si$: 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: $R_f = 0.73$, CH_2Cl_2/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 μm, 250 mm × 10 mm, H_2O/MeCN 40:60, 1 mL/min) failed: mp 158−160 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −40 (*c* 0.16, $CHCl_3$); IR ν_{max} 3450, 1740, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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, $J = 16.1$, 6.1 Hz, 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, $CDCl_3$) 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/z* 868.6 $[M + 23]^+$. Anal. Calcd for $C_{43}H_{59}NO_{16}$: 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 $NaBH_4$ (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 (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −19 (*c* 0.14, $CHCl_3$); IR ν_{max} 3500−3400, 1736, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 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, 5.6 Hz, 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* = 8.5 Hz, 1H), 6.16−6.21 (m, 1H), 6.31 (s, 1H), 7.44−8.22 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{43}H_{61}NO_{16}$: 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, CH_2Cl_2/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 μm, 250 mm × 10 mm, H_2O/MeCN 30:70, 1 mL/min) failed: mp 117−121 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −115 (*c* 0.200, $CHCl_3$); IR ν_{max} 3700−3150, 1737, 1713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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); ^{13}C 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 $C_{45}H_{63}NO_{16}$: 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 $NaBH_4$ (1.2 mg, 0.032 mmol) of the formyl group on **14** (110 mg, 0.111mmol) 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, CH_2Cl_2/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, CH_2Cl_2/MeOH, 9:1). It is possible to isolate pure **17** by semipreparative HPLC (reversed-phase column, 150 Å, 5 μm, 250 mm × 10 mm, H_2O/MeCN 40:60, 1 mL/min). Pure isomer: mp 127−130 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −58 (*c* 0.30, $CHCl_3$); IR ν_{max} 3700−3150, 1713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{43}H_{59}NO_{15}$: 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, CH_2Cl_2/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 CH_2Cl_2 (3 × 20 mL). The organic layer was washed with $NaHSO_4$ (2 M) to pH 2, then with $NaHCO_3$ (5%, 50 mL), and finally with brine (50 mL). After drying over Na_2SO_4 and evaporation of the solvent, the crude product was purified by silica gel column chromatography (EtOAc/cyclohexane = 1:1; R_f = 0.33, CH_2Cl_2/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, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{52}H_{67}NO_{18}$: 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 (SiO_2: EtOAc/cyclohexane, from 1:3 to 3:5; R_f = 0.43, CH_2Cl_2/MeOH, 9:1). It is possible to isolate pure **21** by semipreparative HPLC (reversed-phase column, 150 Å, 5 μm, 250 mm × 10 mm, H_2O/MeCN 40:60, 1 mL/min). Pure isomer: mp 145−147 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −52 (*c* 0.30, $CHCl_3$); IR ν_{max} 3700−3150, 1737, 1713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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,

5H); ^{13}C (125 MHz, $CDCl_3$) 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 $C_{45}H_{65}NO_{17}$: 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 $NaBH_4$ (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, CH_2Cl_2/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, CH_2Cl_2/MeOH, 10:1): mp 143 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −9 (*c* 0.3, $CHCl_3$); IR ν_{max} 377−3150, 1740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) 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 $C_{43}H_{61}NO_{16}$: 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. ^{1}H and ^{13}C 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**; ^{1}H and ^{13}C NMR spectra for compounds **4a**,**b**, **5a**,**b**, **6**, **7b**, **8a**,**b**, and **10**−**22**; HPLC data for compounds **8a**,**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