The Reductive Fragmentation of 7-Hydroxy-9,10-dioxotaxoids

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Dedicated to Professor Paola Vita-Finzi on the occasion of her 70th birthday

Keywords: Antitumour agents / Natural products / Taxoids / Terpenoids

The retro-aldol reductive fragmentation of different structural types of 7-hydroxy-9,10-dioxotaxoids was investigated, showing that the reaction is typical of taxanes and requires cerium(III) promotion with $NaBH_4$ in protic medium and alkylboron (aluminium) hydrides in aprotic solvents. The resulting 7,8-*seco*-taxanes are key intermediates for the synthesis of a novel class of anticancer taxanes endowed with a unique pattern of in vivo biological activity.

Introduction

The retro-aldol epimerisation of the 7-hydroxy group of Taxol (paclitaxel) from a β-equatorial to an α-axial orientation is one of the first reactions described for this anticancer drug,[1] and is typical of baccatin III (**1a**) derivatives.[2] Under mildly basic conditions, the aldol motif bridging rings B and C equilibrates with a C-*seco* aldehyde enolate, which then re-aldolises mainly to the 7-α epimer, stabilised by intramolecular hydrogen bonding between the 7-hydroxy and the 4-acetate carbonyl groups (**1b**, Figure 1, A).[3] This epimerisation takes place under physiological conditions,[4] and is a major problem for the formulation of anticancer taxoids.[5]

The *seco*-aldehyde enolate re-aldolises too rapidly to allow its trapping or spectroscopic detection, but we reasoned that the replacement of the 10-acetoxy group with a carbonyl should stabilise the enolate by conjugation, making it possible to trap the fledging *seco*-aldehyde intermediate in a nucleophilic and/or reductive fashion (Figure 1, B). Indeed, we have reported in a preliminary communication that treatment of an epimeric mixture of 10-deacetyl-10-dehydrobaccatins (**2a/b**) with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ gave, in modest yield, the C-*seco*-taxoid **3a**,[6] which was next elaborated into a series of Taxol analogues by esterification of the 13-hydroxy group with various phenylisoserine and norstatin amino acidic side chains.[7] One of these compounds, the *N*-BOC-norstatin ester **3b** (IDN, 5390), showed cytotoxicity and tubulin binding similar to those of Taxol, and was selected for further biological evaluation.[7] In vivo assays of **3b** in xenografted nude mice showed high antimetastatic and cytostatic activity, coupled with a surprisingly low toxicity.[8] This unique biological profile qualifies **3b** as a new and interesting anticancer candidate, and prompted us to investigate the reductive fragmentation of taxanes **2a/b** further, optimising the yield of the *seco* compound **3a**, and exploring the extension of this reaction to other structural types of taxoids.

Results and Discussion

1. Synthesis of the Reductive Fragmentation Precursors 2a/b and 9

The 9,10-α-diketone motif is rare in natural taxoids,[9] but its corresponding ketol version is present in 10-deacetylbaccatin III (10-DAB III, **4a**). This compound is available in multigram amounts from the leaves of the European yew,[10] and was selected as a starting material for this study. Oxidative remodelling of the α-ketol system of **4a** could be effected by autoxidation in the presence of Cu^{II} salts (Scheme 1). The autoxidation of **4a** occurs selectively at the allylic 13-hydroxy group,[11] but the presence of Cu^{II} salts redirects the reaction to the allylic ketolic hydroxy group, in accordance with the chemoselectivity observed in the Cu^{II}-mediated autoxidation of corticosteroids.[12] Only trace amounts (< 5%) of the 10,13-didehydro derivative **5** were obtained, while extensive epimerisation at C-7 was observed, resulting in the formation of a ca. 3:1 mixture of

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  DOI: 10.1002/ejoc.200300376

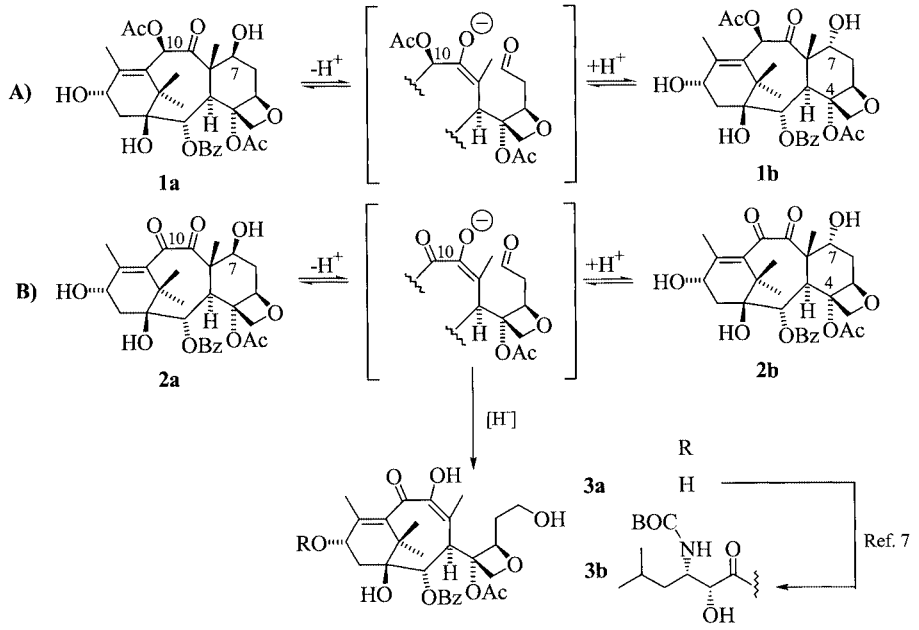
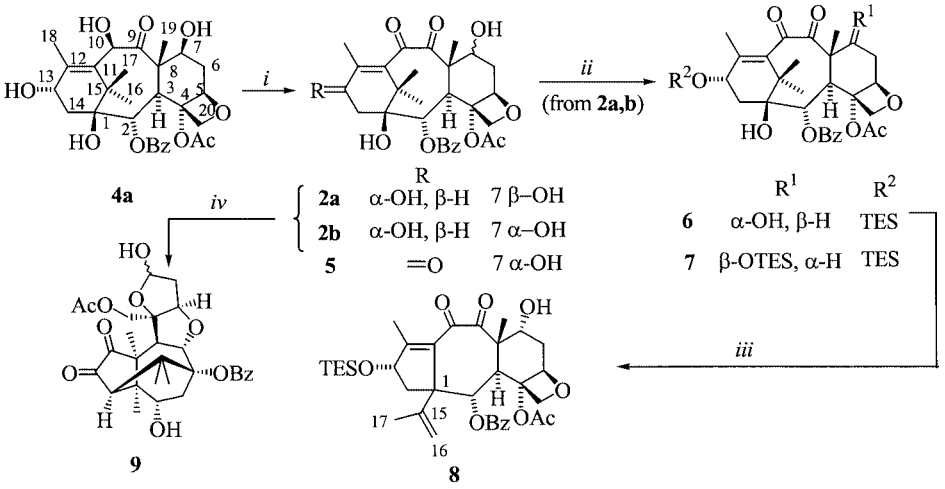


Figure 1. The retro-aldol epimerization of baccatin III derivatives and its exploitation for the synthesis of C-*seco*-taxoids

epimers at this carbon (**2a/b**). Attempts to separate the mixture by gravity column chromatography afforded the pure 7α epimer **2b**, while purification of the 7β epimer **2a** proved elusive on account of its configurational instability under chromatographic conditions. While the 7α epimer **2b** was stable in solvents spanning a wide range of polarity (from $CHCl_3$ to methanol), partially purified samples of the 7β epimer eventually transformed into the 7α epimer both in solution and under prolonged chromatographic conditions, showing that the epimerisation is essentially irreversible. The 7α-hydroxy group of baccatin V is engaged in fairly strong intramolecular hydrogen bonding with the 4-acetate, which stabilises its axial configuration.[3] The observation that the 10,13-didehydro derivative **5** was obtained in a diastereomerically pure 7α-hydroxy configuration backs up the idea that the 13α-hydroxy group of baccatin derivatives can compete with the 7α-hydroxy group for the formation of intramolecular hydrogen bonding with the 4-acetate, and therefore has a long-range stabilising effect on the β configuration of the 7-hydroxy group.[13]

On account of the strong intramolecular hydrogen bonding, the 7α-hydroxy group of **2b** is essentially unreactive in acylation and silylation reactions, and its cryptic nature was exploited for the synthesis of an 11(15→1)abeotaxane precursor for the reductive fragmentation (Scheme 1). Thus, treatment with triethylsilyl chloride (TES-Cl) converted **2a/b** into a mixture of two products, which could be easily separated by chromatography. The major one (**6**, 49−58%) was the 13-TES derivative of **2b**, accompanied by variable minor amounts (3−7%) of the 7,13-diTES derivative of 10-dehydroDAB III (**7**). The low reactivity of the 13α-hydroxy group of taxanes is essentially due to intramolecular hydro-



Scheme 1. Synthesis of taxoid precursors for the reductive fragmentation: (i) $Cu(OAc)_2 \cdot H_2O$, MeOH (75% **2a/b**, 2.5% **5**), (ii) TES-Cl, imidazole, CH_2Cl_2 (53% **6**, 3% **7**), (iii) $SOCl_2$, pyridine, CH_2Cl_2 (80%), (iv) DBU, toluene, 95% (see ref.[15])

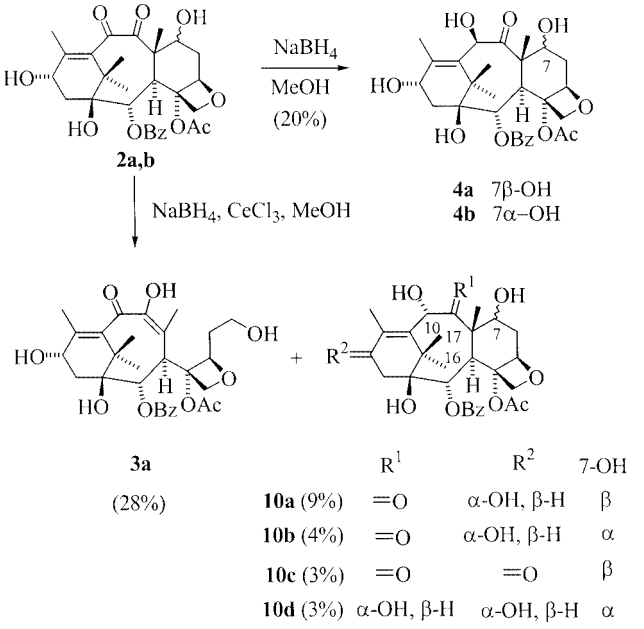
gen bonding with the 4-acetate carbonyl moiety.[14] The engagement of this carbonyl moiety in hydrogen bonding with the 7α-hydroxy group leaves the 13-hydroxy group uncomplexed and reactive, thus explaining the diastereomeric kinetic resolution observed in the silylation of **2a/b**. The choice of the base employed in the silylation was important. While the epimeric mixture **2a/b** is stable in the presence of imidazole, stronger bases such as triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) triggered a spectacular rearrangement to lactols **9**.[15] The 7-unprotected silyl ether **6a** was next treated with $SOCl_2$/pyridine to effect the Wagner−Meerwein rearrangement of the A,B ring system,[16] cleanly affording the 11(15→1)abeotaxane **8**, a suitable substrate for the reductive fragmentation (Scheme 1).

2. Reductive Fragmentation of Taxoids of the 9,10-Dioxo Type

The reductive fragmentation was investigated and optimised with the diastereomeric mixture of 9,10-dioxotaxanes **2a/b**. Reduction with $NaBH_4$ in alcohols (methanol, ethanol, 2-propanol) was practically instantaneous, and gave a mixture with 10-deacetylbaccatin III (**4a**) as the major component (ca. 20% isolated yield), the result of reduction of the 10-carbonyl and reepimerisation at C-7 (Scheme 2). The same result was obtained when starting from the pure 7α epimer **2b**, and in both cases only traces of the more stable 7α epimer **4b** could be detected in the reaction mixture by ^1H NMR or TLC analysis. These observations showed that reduction of the starting α-diketone was faster than retroaldolisation of the *seco*-aldehyde intermediate. Attack at the allylic and less hindered 10-carbonyl was not unexpected, owing to the hindered nature of the 9-keto group of taxanes.[17] On the other hand, the overall stereochemical course of the reaction was surprising. Thus, under the same conditions, a 2,7-disilylated derivative of taxol exclusively gave the unnatural 10-α alcohol,[18] while 10-deacetylbaccatin III (**4a**) is known to equilibrate with its 7α epimer **4b** under mildly basic conditions, such as those expected in the course of a borohydride reduction.[4]

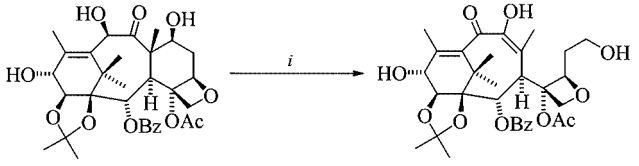
The reducing properties of $NaBH_4$ can be substantially modified by various additives, especially metal ions.[19] In the absence of a clear mechanistic rationale to pursue, the effect of various metal additives on the borohydride reduction of **2a/b** was investigated. Addition of $NiCl_2$, $CoCl_2$ or CuBr did not significantly alter the course of the reduction. Conversely, lanthanides ($CeCl_3 \cdot 7H_2O$, $ScOTf_3$, $YbOTf_3$), especially cerium trichloride, had a dramatic redirecting effect on the course of the reaction. The long-sought reductive fragmentation product **3a** could be isolated in 28% yield (reaction scale: 5 g **2a/b**), accompanied by four minor compounds with an intact taxane skeleton **10a**−**d**, obtained in 9%, 4%, 3% and 3% yields, respectively (Scheme 2).

The structure elucidation of **10a**−**d** was straightforward. The presence of a 7-oxymethine showed that the taxane core had remained intact, while the β-orientation of the 10-hydrogen in **10a**−**d** and of the 9-hydrogen in **10d** was evidenced by NOE experiments, which established a *syn* relationship between these proton(s) and the 19- and 16-methyls. As to the configuration of the 7-hydroxy group, inspection of the splitting pattern of the corresponding methine allowed a straightforward assignment, with H-7 resonating as a well spaced doublet of doublets (J = ca. 10 and 7 Hz) when axial (α), and as a narrow doublet of doublets ($J \approx 4$ and 2 Hz) when equatorial (β). The 10α-hydroxy group apparently overrides the 7α-hydroxy group as hydrogen-bonding donor to the 4-acetate, thus explaining the prevalence of the 7β configuration in the epimers from the unnatural 10α series (**10a/b**). The 13-dehydro derivative **10c** is presumably derived from **10a** by air oxidation[11] during workup or chromatographic purification of the reduction mixture. Compound **3a** showed only broad humps in its NMR spectra. Eventually, all ^1H NMR signals and most ^{13}C resonances could be detected and assigned by working at 130 °C in [D_6]DMSO.[6] These data showed that the α-diketone moiety was completely tautomerised to a diosphenol form. Since extensive line-broadening was also observed in the peracetyl and persilyl derivatives of **3a**,[6] a conformational process is responsible for the dynamic equilibrium evidenced by the NMR spectra. Modification of the 1-hydroxy group had a dramatic slowing effect on the process. Thus, if the reaction sequence to **3a** from **4a** was repeated starting from the 1,14-acetonide **11**,[20] a *seco*-taxane was obtained (**12**, Scheme 3), its NMR spectra showing two sets of sharp lines at room temperature, in a ca. 3:2 ratio. The NMR spectra of **12** were amenable to full assignment by 2D measurements (HMQC, HMBC). In the ^1H NMR spectrum, the major differences relate to the signals of the oxetane-containing chain at C-3 and the allylic methyl C-19, with inter-rotameric differences larger than 0.5 ppm for the proton signals of the 4-acetate, one of the diastereotopic 20-methylene protons and the 19-methyl group. The major



Scheme 2. Treatment of 10-dehydro-10-deacetylbaccatin (**2a/b**) with $NaBH_4$

difference evidenced by NOE difference experiments is the lack of correlation between the 19-methyl group and one of the oxetane protons in the minor rotamer. Taken together, these observations suggest that rotation around the C-3/C-4 bonds plays a key role in the conformational equilibration of C-*seco*-taxanes, while reduction of the mobility around the C-1/C-14 bond slows down the conformational equilibration, making it possible to observe the signals of species differing in the orientation of the oxetane ring with respect to the bicyclic diterpene core. The reasons for the high barrier of rotation around the C-3/C-4 bond in C-*seco*-taxoids is unclear. It is worth noting that related compounds devoid of the oxetane ring and the diosphenol system are intermediates in Wender's synthesis of Taxol, but no dynamic process was reported for them.[21] One C,D-bis(*seco*-taxane) obtained from 7-dehydro-13-acetylbaccatin III was also reported to have normal NMR spectra.[22]



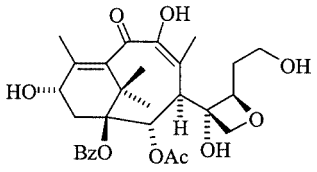
Scheme 3. Synthesis of the *seco*-acetal **12**: (i) 1. $Cu(OAc)_2 \cdot H_2O$, MeOH, 2. $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (overall 21%)

The beneficial effect of cerium trichloride on the retro-aldol reductive trapping is counterintuitive, since the process involves the reduction of an aldehyde in the presence of a ketone, and addition of $CeCl_3$ has been shown to have an opposite effect on the reduction of ketoaldehydes.[23] A possible interpretation is that the diosphenolate moiety strongly chelates cerium(III), producing a relatively stable complex and a reduction in its nucleophilicity large enough to permit the reductive trapping of the fledging 7-aldehyde before retro-aldolisation. A full equivalent of $CeCl_3$ was indeed necessary for the reaction, as would be expected of a stoichiometric interaction of the additive with the substrate and/or the reduction product.

While providing sufficient material to allow the elaboration of **3a** into a series of antitumour taxoids, the cerium-promoted reductive fragmentation suffered from several drawbacks. On the one hand, its yield was modest, and the formation of a mixture made a careful chromatographic step necessary for the purification of **3a**. Furthermore, the reaction could not be applied to taxanes bearing amino acidic chains at C-13, since loss of the side chain was observed. Protection of the 2′-hydroxy group as a silyl ether could only reduce, not completely prevent, this loss during the reductive fragmentation.[24] Clearly another approach was needed to fuel additional biological studies on **3b** and sustain a significant structure-activity study for this novel class of anticancer compounds.

Modified borohydrides were first examined. With $NaBH_3CN$, reduction of the 10-keto group and counter-thermodynamic equilibration at C-7 were observed, 10-DAB III (**4a**) being obtained as the only reaction product (56%). With $Zn(BH_4)_2$, a mixture of the C-*seco* compound **3a** (11%) and unchanged **2b** was obtained. However, our efforts to increase the conversion failed, since **2b** was stable in the presence of $Zn(BH_4)_2$, and epimerization at C-7 was apparently shut down under these reaction conditions. Raney nickel has been reported to reduce aldehydes in the presence of ketones,[25] but with **2a/b** only reduction of the 10-keto group and counter-thermodynamic epimerisation at C-7 were observed, **4a** being obtained as the only reaction product (41%).

Complex alanes and boranes gave remarkable results, which eventually resulted in an optimised reductive fragmentation procedure. While the alkoxyalane Red-Al gave **4a** as the major reaction product (59%), alkyl alanes and boranes such as DIBAL and L- and K-selectrides afforded the C-*seco* compound **3a** as the major or the exclusive reaction product. The reaction with L-selectride was especially clean and was further investigated, with optimisation of various parameters (temperature, concentration) and the workup. Thus, a temperature of −15 °C turned out to be an excellent compromise between the sluggish reactivity observed at −78 °C and the formation of the acyl rearranged product **13** when the reaction was carried out at room temperature. Although the formation of **13** was modest (ca. 5−10%), it significantly complicated the purification of **4a**, owing to its similar chromatographic mobility. On the other hand, conventional oxidative workup[26] of the selectride reaction mixture resulted in the complete degradation of **3a**, presumably because of its sensitivity to oxidants, while an acidic workup followed by a quick purification by gravity column chromatography was able to provide the C-*seco* diosphenol taxane **3a** in 90% yield (reaction scale: 5 g **2a/b** as starting material). The different behaviour of the alkoxyalane Red-Al from the alkylalane DIBAL and the alkylboranes K- and L-selectrides is remarkable and presumably related to differences in oxyphilicity. Owing to the presence of two oxygen ligands, the aluminium core of Red-Al might not bind the diosphenolate moiety strongly enough to prevent intramolecular aldol trapping of the fledging *seco*-aldehyde intermediate at the expenses of intermolecular hydride trapping.



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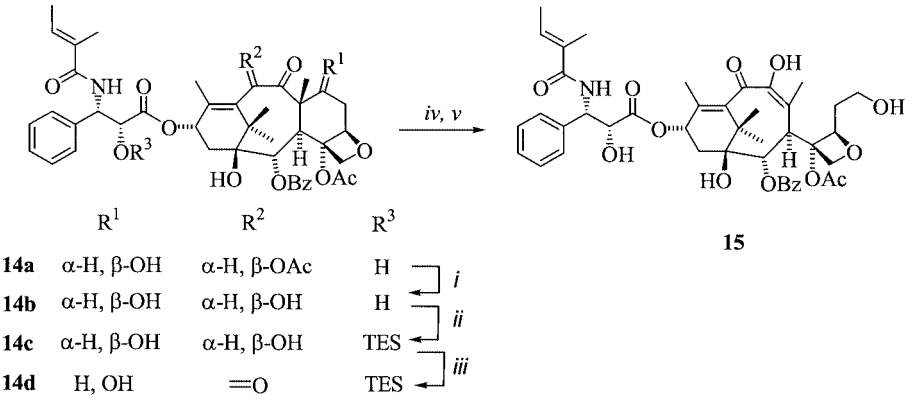
The L-selectride reductive fragmentation could also be carried out on 2′-protected 9,10-dioxotaxanes bearing amino acidic side chains, as exemplified by the conversion of cephalomannine (**14a**),[27] a side product of the isolation of



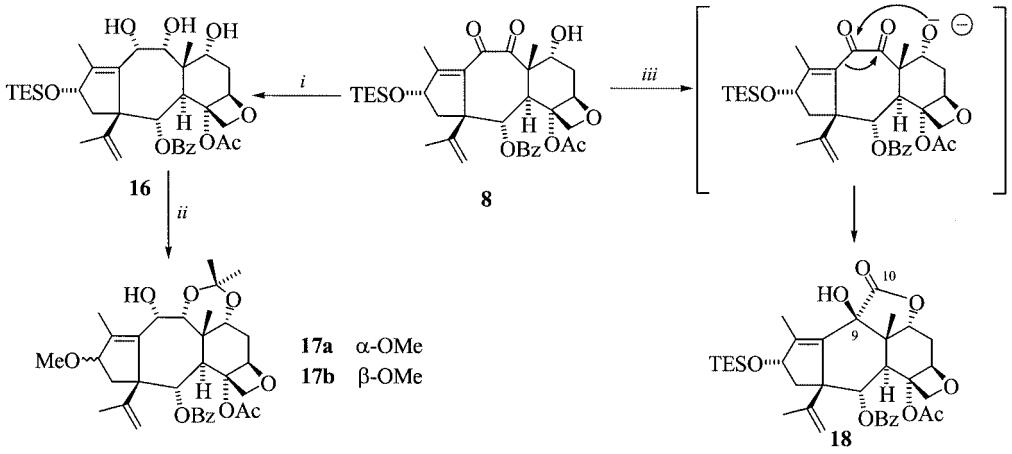
Scheme 4. Synthesis of the C-*seco*-taxane**15** from cephalomannine (**14a**): (i) H_2O_2, $NaHCO_3$ (88%), (ii) TES-Cl, imidazole, DMF (51%), (iii) $Cu(OAc)_2.H_2O$, MeOH, (iv) ^{l}-selectride, THF, (v) HCl, MeOH (47% from **14d**)

Taxol, into its corresponding C-*seco*-taxane **15** (Scheme 4). After chemoselective deacetylation of the 10-hydroxy group,[28] the 2′-hydroxy group was protected as a TES ether, and the α-ketol system was subjected to autoxidation conditions in the presence of $Cu(OAc)_2$. The reductive fragmentation was then uneventful, affording, after deprotection, **15** in overall 21% yield from **14a**.

Application of both reductive fragmentation procedures to the 11(15→1)abeobaccatin **8** failed to afford compounds of the C-*seco* type. Thus, treatment with the $NaBH_4$/$CeCl_3{\cdot}7H_2O$ system in methanol gave the triol **16** as the only reaction product (89% yield), the result of a twofold hydride attack from the β-face of the molecule (Scheme 5). Compound **16** showed rather broad NMR spectra, a feature not unusual in 11(15→1)abeotaxanes,[29] and its structure elucidation was confirmed by its conversion into the cyclic acetonides **17a/b** by treatment with 2,2-dimethoxypropane and acids. Two aspects of the acetalisation were somewhat unexpected, namely the formation of a six-membered acetonide rather than the expected dioxolane derivative of the *cis*-diol system, and the solvolytic replacement of the 13-silyl ether by a methyl ether, with methanol being released in the ketalisation step. On the other hand, treatment with L-selectride gave the γ-lactone **18** as the only reaction product. Owing to the highly congested environment, it is not inconceivable that the α-diketone system of the abeotaxane **8** resists reduction by L-selectride, a bulky reagent, rather undergoing an alkoxide-induced benzil rearrangement. The benzil rearrangement is not unprecedented in 9,10-dioxotaxoids.[15,30] Whatever the mechanism is, the transformation of **8** into **18** adds to the growing and puzzling inventory of non-reductive reactions observed upon treatment of taxoids with metal hydrides.[31]

Conclusions

The chemistry presented here testifies vividly to our limited predictive capacity in the realm of multifunctional compounds. A procedure for the reductive fragmentation of 9,10-dioxotaxoids with 10-deacetyl-10-dehydrobaccatin III (**2a/b**) as a model compound has been developed. While of immediate relevance for the synthesis of the drug candidate IDN 5390 (**3b**), the solution turned out to be very ad hoc, and not even applicable to compounds closely related to **2a/b**. The intriguing biological profile of C-*seco*-taxoids justifies efforts to optimise their synthesis, and the solution of the problem came as a result of a "shotgun" approach, which raises a series of intriguing mechanistic issues of



Scheme 5. Attempted reductive fragmentation of the abeotaxane **8**: (i) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH (98%), (ii) dimethoxypropane, PTSA (45%), (iii) L-selectride, THF (18%)

more general relevance and worth further investigation in other multifunctional molecular assemblies.

Experimental Section

General: Column chromatography: Merck silica gel. IR: Shimadzu DR 8001 spectrophotometer. NMR: Bruker DRX 500 (500 MHz and 125 MHz for ^1H and ^{13}C, respectively). The spectra were recorded in C_6D_6, $CDCl_3$, [D_6]DMSO, or [D_4]MeOH, and the solvent signals (δ = 7.22/128.39, 7.26/77.0, 2.49/39.7, and 3.35/49.3 ppm respectively) were used as reference. The chemical shifts (δ) are given in ppm, and the coupling constants (*J*) in Hz. COSY, HMQC, and HMBC experiments were recorded with gradient enhancements by use of sine-shaped gradient pulses. For the 2D heteronuclear correlation spectroscopy, the refocusing delays were optimised for $^1J_{C,H}$ = 145 Hz and $^nJ_{C,H}$ = 10 Hz. The crude data were transformed and the spectra were evaluated with the standard Bruker XWIN NMR software (rev. 010101). CH_2Cl_2 was dried by distillation from CaH_2, and THF from distillation from Na/benzophenone. Na_2SO_4 was used to dry solutions before the evaporation. Reactions were monitored by TLC on Merck 60 F_{254} (0.25 mm) plates, which were visualised by UV inspection and/or by staining with 5% H_2SO_4 in ethanol and heating. Taxoids retain solvents strongly, and are not amenable to elemental analysis.

Copper(II)-Mediated Autoxidation of 10-Deacetylbaccatin III (4a): In a 1-L two-necked flask, **4a** (2 g, 3.7 mmol) was suspended in methanol (150 mL), and $Cu(OAc)_2H_2O$ (5 g) was added in small portions, with vigorous mechanical stirring, over ca. 10 min. The pale blue suspension darkened during the course of the reaction, and stirring was continued with the flask neck unstoppered to allow contact with air. After 72 h, the reaction mixture was worked up by concentration and addition of water (200 mL) and EtOAc (350 mL), dissolving most of the voluminous precipitate. The organic phase was washed with 2 N NH_3 to remove copper salts, and then with brine. After drying (Na_2SO_4) and evaporation, the residue was purified by column chromatography on silica gel, with a petroleum ether/EtOAc gradient. Fractions eluted with petroleum ether/EtOAc (5:5) afforded 50 mg (2.5%) of **5**. Those eluted with petroleum ether/EtOAc (3:7) gave **2b** (100 mg, 5%) and a mixture of **2a** and **2b** (1.4 g, ca. 1:3 as evidenced by ^1H NMR spectroscopy; overall yield of **2a/b**: 75%).

10,13-Bis(dehydro)-10-deacetylbaccatin V (5): White powder, m.p. 183−185 °C. IR (KBr): $\tilde{\nu}$ = 3581, 3453, 3303, 1716, 1709, 1668, 1277, 1115, 1053, 1005, 711 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.14 (s, 16-H/3), 1.26 (s, 17-H/3), 1.70 (s, 19-H/3), 1.88 (s, 18-H/3), 2.27 (s, OAc), 2.74 (d, *J* = 15.5 Hz, 14b-H), 3.12 (d, *J* = 15.5 Hz, 14a-H), 3.85 (ddd, *J* = 10, 5, 3 Hz, 7-H), 4.12 (d, *J* = 7.1 Hz, 3-H), 4.27(d, *J* = 8.3 Hz, 20b-H), 4.29 (d, *J* = 9.2 Hz, 7-OH), 4.44 (d, *J* = 8.3 Hz, 20a-H), 4.89 (m, 5-H), 5.91 (d, *J* = 7.1 Hz, 2-H), 7.52 (BB′-Bz), 7.66 (C-Bz), 8.09 (AA′-Bz) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.2 (C-19), 15.4 (C-18), 23.9 (C-16), 23.1 (OAc), 33.8 (C-17), 34.4 (C-6), 37.4 (C-15), 41.1 (C-3), 41.4 (C-14), 60.2 (C-8), 75.0 (C-2), 77.9 (C-7), 77.9 (C-20), 81.42 (C-4), 83.2 (C-1), 84.2 (C-5), 130.5 (Bz), 130.9 (Bz), 132.4 (Bz), 136.3 (Bz), 141.5 (C-12), 160.3 (C-11), 168.9 (Bz), 174.1 (OAc), 189.4 (C-10), 199.9 (C-13), 208.5 (C-9) ppm. HRMS (70 eV): *m*/*z* = 540.2008 (calcd. for $C_{29}H_{32}O_{10}$, 540.1996).

10-Dehydrobaccatin V (2b): White powder, m.p. 162 °C. IR (KBr): $\tilde{\nu}$ = 3420, 1720, 1265, 1100, 1070, 1010, 720 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.09 (s, 17-H/3), 1.10 (s, 16-H/3), 1.72 (s, 19-H/3), 1.97 (br. s, 18-H/3), 2.39 (s, OAc), 3.86 (ddd, *J* = 10, 5, 3 Hz, 7-H), 4.11 (d, *J* = 7.1 Hz, 3-H), 4.32 (d, *J* = 8.3 Hz, 20b-H), 4.45 (d, *J* = 9.2 Hz, 7-OH), 4.44 (d, *J* = 8.3 Hz, 20a-H), 4.94 (m, 13-H + 5-H), 5.84 (d, *J* = 7.1 Hz, 2-H), 7.51 (BB′-Bz), 7.59 (C-Bz), 8.14 (AA′-Bz) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6 (C-18), 15.0 (C-19), 22.1 (C-16), 22.5 (OAc), 26.3 (C-17), 35.3 (C-6), 38.9 (C-14), 39.8 (C-15), 39.6 (C-3), 57.3 (C-8), 67.5 (C-13), 77.3 (C-7), 74.9 (C-2), 77.2 (C-20), 79.0 (C-1), 81.2 (C-4), 82.5 (C-5), 128.8 (Bz), 129.2 (Bz), 130.1 (Bz), 133.9 (Bz), 140.5 (C-11), 146.6 (C-12), 167.1 (Bz), 172.5 (OAc), 189.2 (C-10), 208.4 (C-9 ppm. HRMS (70 eV): *m*/*z* = 542.2155 (calcd. for $C_{29}H_{34}O_{10}$, 542.2152).

Silylation of 10-Dehydro-10-deacetylbaccatin (2a/b): Imidazole (753 mg, 11.1 mmol, 4 mol equiv.) and TES-Cl (1 M in CH_2Cl_2, 11.1 mL, 11.1 mmol, 4 mol equiv.) were added to a solution of a ca. 1:3 mixture (^1H NMR analysis) of 10-dehydro-10-deacetylbaccatins III and V (1.5 g, 2.77 mmol) in dry CH_2Cl_2 (16.6 mL). After stirring overnight at room temperature, the reaction mixture was worked up by dilution with EtOAc and washing with 2 N H_2SO_4. After washing with brine, drying (Na_2SO_4) and evaporation, the residue was purified by column chromatography on silica gel (34 g) eluted with a petroleum ether/EtOAc gradient (9:1 to 3:7), affording **7** (56 mg, 3%), **6** (956 mg, 53%) and starting material (108 mg).

13-TES-10-dehydro-10-deacetylbaccatin V (6): Foam. IR (KBr): $\tilde{\nu}$ = 3496, 1711, 1696, 1267, 1244, 1125, 936, 889 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.61 (q, *J* = 7.9 Hz, OTES), 0.70 (q, *J* = 7.9 Hz, OTES), 0.97 (t, *J* = 7.9 Hz, OTES), 1.03 (t, *J* = 7.9 Hz, OTES), 1.20 (s, 16-H/3), 1.57 (s, 17-H/3), 1.70 (s, 19-H/3), 2.03 (br. s, 18-H/3), 2.30 (s, OAc), 3.65 (d, *J* = 7.2 Hz, 3-H), 4.20 (dd, *J* = 10, 3 Hz,, 7-H), 4.18 (d, *J* = 8.2 Hz, 20b-H), 4.33 (d, *J* = 8.2 Hz, 20a-H), 5.00 (br. t, *J* = 7.5 Hz, 13-H), 4.92 (br. d, *J* = 9 Hz, 5-H), 5.76 (d, *J* = 7.2 Hz, 2-H), 7.49 (BB′-Bz), 7.65 (C-Bz), 8.11 (AA′-Bz) ppm. HRMS (70 eV): *m*/*z* = 770.3897 (calcd. for $C_{41}H_{62}O_{10}Si_2$, 770.3882).

7,13-DiTES-10-dehydro-10-deacetylbaccatin III (7): Foam. IR (KBr): $\tilde{\nu}$ = 3462, 1717, 1451, 1107, 1007, 986, 712 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.69 (q, *J* = 7.9 Hz, OTES), 1.02 (t, *J* = 7.9 Hz, OTES), 1.11 (s, 16-H/3), 1.16 (s, 17-H/3), 1.71 (s, 19-H/3), 1.94 (br. s, 18-H/3), 2.39 (s, OAc), 3.85 (br. d, *J* = 10 Hz, 7-H), 4.02 (d, *J* = 7.4 Hz, 3-H), 4.31 (d, *J* = 8.2 Hz, 20b-H), 4.43 (d, *J* = 8.2 Hz, 20a-H), 4.57 (d, *J* = 10 Hz, OH), 4.96 (m, 5-H + 13-H), 5.82 (d, *J* = 7.4 Hz, 2-H), 7.51(BB′-Bz), 7.70 (C-Bz), 8.11 (AA′-Bz) ppm. HRMS (70 eV): *m*/*z* = 656.3003 (calcd. for $C_{35}H_{48}O_{10}Si$, 656.3017).

Wagner−Meerwein Rearrangement of 13-TES-10-dehydro-10-deacetylbaccatin V (6): Dry pyridine (3.0 mL, 2.9 g, 37.1 mmol, 24.4 mol equiv.) and thionyl chloride (757 μL, 1.24 g, 10.4 mmol, 6.8 mol equiv.) were added to a cooled (0 °C) solution of **6** (1.0 g, 1.52 mmol) in dry CH_2Cl_2 (18 mL). After stirring for 5 min at 0 °C, the reaction mixture was worked up by dilution with EtOAc and neutralisation with satd. $NaHCO_3$. After washing with 2 N H_2SO_4 and brine, the organic phase was dried (Na_2SO_4) and the solvents were evaporated. The residue was purified by column chromatography on silica gel (25 g, elution with petroleum ether/EtOAc, 8:2) to afford crude **8** (780 mg, 80%).

13-TES-10-deacetyl-10-dehydro-11(15→1)abeobaccatin V (8): Foam. IR (KBr): $\tilde{\nu}$ = 3492, 1719, 1672, 1603, 1372, 1260, 1105, 853, 716 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.56 (q, *J* = 7.9 Hz, OTES), 0.98 (t, *J* = 7.9 Hz, OTES), 1.68 (s, 19-H/3), 1.72 (br. s, 16-H/3), 2.16 (s, OAc + 18-H/3), 3.88 (d, *J* = 8.2 Hz, 3-H), 4.02 (m, 7-H), 3.56 (d, *J* = 8.4 Hz, 20b-H), 4.09 (d, *J* = 9 Hz, OH), 4.42 (d, *J* = 8.4 Hz, 20a-H), 4.50 (br. t, *J* = 7.5 Hz, 13-H), 4.64 (br. s, 17b-H), 4.75 (br. s, 17a-H), 4.99 (br. d, *J* = 7 Hz, 5-H), 5.82 (d, *J* = 8.2 Hz,

2-H), 7.49 (BB′-Bz), 7.63 (C-Bz), 8.03 (AA′-Bz) ppm. HRMS (70 eV): *m/z* = 638.2919 (calcd. for $C_{35}H_{46}O_9Si$, 638.2911).

Reductive Fragmentation of 10-Dehydro-10-deacetylbaccatin (III + V) (2a/b) with $NaBH_4/CeCl_3$: $NaBH_4$ (ca. 600 mg) was added portionwise to a stirred suspension of **2a/b** (5 g, 9.2 mmol) and $CeCl_3{\cdot}7H_2O$ (3.4 g, 9.2 mmol, 1 mol equiv.) in methanol (300 mL) until TLC (petroleum ether/EtOAc, 1:9) showed the disappearance of the starting material. The reaction was then worked up by the addition of satd. NH_4Cl (300 mL) and extraction with EtOAc (3 × 200 mL). The organic phase was washed with brine and dried (Na_2SO_4), and the solvents were evaporated, affording a white powder, which was purified by column chromatography on silica gel (250 g), with use of a petroleum ether/EtOAc gradient. Fractions eluted with petroleum ether/EtOAc (7:3) afforded **10c** (150 mg, 3%), **10a** (450 mg, 9%), **10b** (200 mg, 4%) and **10d** (150 mg, 3%). Fractions eluted with petroleum ether/EtOAc (1:9) gave **3a** (1.4 g, 28%).

10-Epi-10-deacetylbaccatin III (10a): White powder, m.p. 128−130 °C. IR (KBr): ṽ = 3410, 1720, 1705, 1250, 1110, 1070, 975, 705 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.13 (s, 17-H/3), 1.15 (s, 16-H/3), 1.69 (s, 19-H/3), 1.90 (m, 6β-H), 2.10 (m, 14-H/2), 2.18 (br. s, 18-H/3), 2.31 (s, OAc), 2.52 (m, 6α-H), 4.18 (d, *J* = 8.3 Hz, 20b-H), 4.26 (d, *J* = 6.8 Hz, 3-H), 4.33 (d, *J* = 8.3 Hz, 20a-H), 4.76 (m, 13-H + 7-H), 5.03 (d, *J* = 8.1 Hz, 5-H), 5.20 (br. s, 10-H), 5.68 (d, *J* = 6.8 Hz, 2-H), 7.49 (BB′-Bz), 7.58 (C-Bz), 8.12 (AA′-Bz) ppm. ^{13}C NMR ([D_6]DMSO): δ = 11.0 (C-19), 14.0 (C-18), 22.5 (C-16), 22.7 (OAc), 26.8 (C-17), 36.3 (C-6), 39.3 (C-14), 43.0 (C-15), 45.2 (C-3), 60.0 (C-8), 66.7 (C-13), 69.9 (C-7), 75.6 (C-2), 76.1 (C-20), 77.1 (C-1), 80.3 (C-4), 82.0 (C-10), 84.2 (C-5), 129.1 (Bz), 129.9 (Bz), 130.7 (Bz), 131.3 (C-11), 133.6 (Bz), 135.5 (C-12), 165.7 (Bz), 169.7 (OAc), 208.4 (C-9) ppm. HRMS (70 eV): *m/z* = 544.2324 (calcd. for $C_{29}H_{36}O_{10}$, 544.2309).

10-Epi-10-deacetylbaccatin V (10b): White powder, m.p. 198−200 °C. IR (KBr): ṽ = 3380, 2250, 1710, 1600, 1270, 1100, 1070, 980, 730 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.04 (s, 17-H/3), 1.06 (s, 16-H/3), 1.66 (s, 19-H/3), 2.18 (br. s, 18-H/3), 2.38 (s, OAc), 3.84 (ddd, *J* = 10, 5, 3 Hz, 7-H), 4.38 (d, *J* = 8.3 Hz, 20b-H), 4.42 (d, *J* = 8.3 Hz, 20a-H), 4.46 (d, *J* = 7.3 Hz, 3-H), 4.68 (m, 13-H), 4.94 (m, 5-H + 10-H), 5.71 (d, *J* = 7.3 Hz, 2-H), 5.98 (d, *J* = 11.3 Hz, 7-OH), 6.09 (d, *J* = 11.6 Hz, 10-OH), 7.52 (BB′-Bz), 7.61 (C-Bz), 8.12 (AA′-Bz) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7 (C-18), 17.1 (C-19), 21.39 (C-16), 22.6 (OAc), 25.7 (C-17), 34.8 (C-6), 38.3 (C-14), 43.0 (C-15), 41.6 (C-3), 59.6 (C-8), 68.5 (C-13), 75.1 (C-7), 76.4 (C-2), 77.7 (C-20), 78.4 (C-1), 81.6 (C-4), 81.2 (C-10), 82.4 (C-5), 128.7 (Bz), 129.4 (Bz), 130.1 (Bz), 130.7 (Bz), 133.7 (Bz), 134.2 (C-11), 134.3 (C-12), 167.1 (Bz), 173.1 (OAc), 211.6 (C-9) ppm. HRMS (70 eV): *m/z* = 544.2327 (calcd. for $C_{29}H_{36}O_{10}$, 544.2309).

13-Dehydro-10-epi-10-deacetylbaccatin III (10c): Amorphous foam. IR (KBr): ṽ = 3453, 1721, 1665, 1603, 1375, 1244, 1178, 1071, 947 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.16 (s, 17-H/3), 1.19 (s, 16-H/3), 1.71 (s, 19-H/3), 2.29 (br. s, 18-H/3), 2.31 (s, OAc), 2.65 (d, *J* = 20 Hz, H-14b), 3.02 (d, *J* = 20 Hz, H-14b), 4.19 (d, *J* = 8.3 Hz, 20b-H), 4.30(d, *J* = 8.3 Hz, 20a-H), 4.39 (d, *J* = 6.8 Hz, 3-H), 4.82(dd, *J* = 7, 4 Hz, 7-H), 4.98 (d, *J* = 8.1 Hz, 5-H), 5.41 (br. s, 10-H), 5.69 (d, *J* = 6.8 Hz, 2-H), 7.50 (BB′-Bz), 7.59 (C-Bz), 8.06 (AA′-Bz) ppm. HRMS (70 eV): *m/z* = 542.2140 (calcd. for $C_{29}H_{34}O_{10}$, 546.2152).

10-Epi-10-deacetyl-9βH-dihydrobaccatin V (10d): Amorphous foam. IR (KBr): ṽ = 3431, 2934, 1716, 1601, 1450, 1373, 1315, 1026, 719 cm^{-1}. ^1H NMR ($CDCl_3$ /[D_6]DMSO, after D_2O exchange): δ = 1.09 (s, 17-H/3), 1.39 (s, 16-H/3), 1.46 (s, 19-H/3), 2.10 (br. s, 18-H/3), 2.29 (s, OAc), 3.84(d, *J* = 7.4 Hz, 3-H), 4.32 (br. s, 9-H), 4.36 (m, 7-H), 4.39 (d, *J* = 8.6 Hz, H-20b), 4.59 (br. s, 10-H), 4.88 (br. s, 13-H), 4.89 (d, *J* = 8.1, 5-H), 5.88 (d, *J* = 7.4 Hz, 2-H), 7.59 (BB′-Bz), 7.63 (C-Bz), 8.10 (AA′-Bz) ppm. HRMS (70 eV): *m/z* = 546.2455 (calcd. for $C_{29}H_{38}O_{10}$, 546.2465).

10-Dehydro-7,8-*seco*-10-deacetylbaccatin III (3a): White powder, m.p. 159−163 °C. IR (KBr): ṽ = 3453, 1751, 1718, 1682, 1647, 1277, 1223, 1131, 1028, 712 cm^{-1}. ^1H NMR (CD_3OD, 50 °C): δ = 1.08 (s, 16-H/3), 1.12 (s, 17-H/3), 1.81 (br. s, 19-H/3), 1.83 (br. s, OAc), 1.91 (br. s, 18-H/3), 1.95 (br. m, 6b-H), 2.36 (br. m,. 14b-H), 2.55 (br. m, 6a-H), 2.81 (br. m, 14a-H), 3.57 (br. m, 7b-H), 3.77 (br. m, 7a-H), 4.21 (d, *J* = 8.3 Hz, 20b-H), 4.29 (d, *J* = 7.5 Hz, 3-H), 4.87 (m, 13-H), 5.15 (d, *J* = 8.3 Hz, 20a-H), 5.27 (br. d, *J* = 8.0 Hz, 5-H), 5.63 (d, *J* = 7.5 Hz, 2-H), 7.52 (BB′-Bz), 7.65 (C-Bz), 8.11 (AA′-Bz) ppm. ^{13}C NMR ([D_6]DMSO, 130 °C): δ = 14.3 (C-19), 14.9 (C-18), 22.0 (OAc), 21.4 (C-16), 24.9 (C-17), 37.1 (C-14), 37.4 (C-6), 43.2 (C-15), 44.4 (C-3), 59.6 (C-7), 69.1 (C-13), 74.8 (C-2), 74.9 (C-20), 80.4 (C-1), 86.2 (C-4), 87.2 (C-5), 124.6 (C-8), 128.4 (Bz), 129.03 (Bz), 129.3 (Bz), 133.9 (Bz), 127.0 (C-12), 142.4 (C-11), 149.6 (C-9), 167.4 (Bz), 169.2 (OAc), 191.2 (C-10) ppm. HRMS (70 eV): *m/z* = 544.2319 (calcd. for $C_{29}H_{36}O_{10}$, 544.2309).

Synthesis of 14-Hydroxy-10-dehydro-7,8-*seco*-10-deacetylbaccatin III 1,14-Acetonide (12): $Cu(OAc)_2{\cdot}H_2O$ (1.2 g) was added in small portions over ca. 5 min to a magnetically stirred suspension of **11**[20] (604 mg, 1 mmol) in methanol (10 mL). After stirring overnight, the reaction mixture was worked up by concentration and addition of water (60 mL) and EtOAc (60 mL). The organic phase was washed with 2 N NH_3 to remove copper salts, and then with brine. After drying (Na_2SO_4) and evaporation, the residue was taken up in methanol (5 mL) and treated with $CeCl_3{\cdot}7H_2O$ (371 mg, 1 mmol, 1 mol equiv.) and next $NaBH_4$ (60 mg). After stirring for 20 min at room temp., the reaction mixture was worked up by the addition of satd. NH_4Cl (30 mL) and extraction with EtOAc (3 × 20 mL). The organic phase was washed with brine and dried (Na_2SO_4), and the solvents were evaporated. The residue was purified by column chromatography on silica gel (25 g), with use of a petroleum ether/EtOAc gradient. Fractions eluted with petroleum ether/EtOAc (3:7) gave a complex mixture of taxanes that was not further characterized, while fractions eluted with petroleum ether/EtOAc (1:9) afforded **12** (124 mg, 21% from **11**) as a white powder. M.p. 109−112 °C. IR (KBr): ṽ = 3432, 1736, 1649, 1269, 1159, 1092, 1026, 714 cm^{-1}. ^1H NMR ($CDCl_3$) Major rotamer: δ = 1.05 (s, acetonide), 1.11 (s, 17-H/3), 1.17 (s, 16-H/3), 1.43 (s, acetonide), 1.72 (s, OAc), 1.82 (br. s, 19-H/3), 2.02 (br. s, 18-H/3), 2.03 (br. m, 6b-H), 2.48 (br. m, 6a-H), 3.83 (br. m, 7b-H), 3.91 (br. m, 7a-H), 4.28 (d, *J* = 8.1 Hz, 20b-H), 4.35 (d, *J* = 7.5 Hz, 3-H), 4.84 (d, *J* = 2 Hz, 14-H), 4.98 (d, *J* = 2 Hz, 13-H), 5.18 (d, *J* = 8.1 Hz, 20a-H), 5.36 (br. d, *J* = 8.0 Hz, 5-H), 6.01 (d, *J* = 7.5 Hz, 2-H), 7.49 (BB′-Bz), 7.59 (C-Bz), 8.00 (AA′-Bz) ppm. Minor rotamer: δ = 1.03 (s, acetonide), 1.13 (s, 17-H/3), 1.13 (s, 16-H/3), 1.39 (s, acetonide), 1.92 (br. s, 18-H/3), 2.00 (br. m, 6b-H and 6a-H), 2.35 (s, OAc),), 2.44 (br. s, 19-H/3), 3.14 (br. m, 7b-H and 7a-H), 4.29 (d, *J* = 2 Hz, 14-H), 4.36 (d, *J* = 8.1 Hz, 20b-H), 4.42 (d, *J* = 8.1 Hz, 20a-H), 4.86 (d, *J* = 7.5 Hz, 3-H), 4.85 (d, *J* = 2 Hz, 13-H), 4.99 (br. d, *J* = 8.0 Hz, 5-H), 5.98 (d, *J* = 7.5 Hz, 2-H), 7.49 (BB′-Bz), 7.62 (C-Bz), 8.16 (AA′-Bz) ppm. ^{13}C NMR ($CDCl_3$): Major rotamer: δ = 14.3 (C-19), 14.7 (C-18), 22.0 (OAc), 22.2 (C-16), 26.8 (C-17), 38.1 (C-6), 42.7 (C-15), 44.5 (C-3), 59.0 (C-7), 63.7 (C-2), 73.4 (C-13), 74.9 (C-20), 90.3 (C-1), 83.5 (C-14), 86.3 (C-4), 86.4 (C-5), 125.0 (C-8), 129.0 (Bz), 129.1 (Bz), 129.5 (Bz), 133.6 (Bz), 137.5 (C-12), 142.5 (C-11), 148.9 (C-9), 165.5 (Bz), 169.1 (OAc), 191.3 (C-10) ppm. Minor rotamer: δ = 13.6 (C-19), 14.3

(C-18), 22.5 (OAc), 21.4 (C-16), 27.2 (C-17), 34.0 (C-6), 42.1 (C-3), 43.2 (C-15), 60.3 (C-7), 69.9 (C-2), 74.7 (C-13), 76.5 (C-20), 89.1 (C-1), 84.1 (C-14), 85.8 (C-4), 85.8 (C-5), 125.0 (C-8), 128.7 (Bz), 129.8 (Bz), 129.9 (Bz), 133.6 (Bz), 138.6 (C-12), 142.5 (C-11), 148.8 (C-9), 165.6 (Bz), 170.0 (OAc), 191.4 (C-10) ppm. HRMS (70 eV): m/z = 600.2588 (calcd. for $C_{32}H_{40}O_{11}$, 600.2571).

Reductive Fragmentation of 10-Dehydro-10-deacetylbaccatin (III + V) (2a/b) with L-Selectride: In a two-necked 250 mL flask, **2a/b** (5.00 g, 9.22 mmol) was suspended in dry THF (100 mL). With vigorous magnetic stirring, the reaction mixture was cooled to −15 °C (bath temperature) while L-selectride (1.0 M in THF, 37 mL, 36.9 mmol, 4 mol equiv.) was added dropwise over ca. 3 min. At the end of the addition, the cooling bath was removed, and the yellow-orange reaction mixture was worked up by the addition of wet EtOAc and 2 N H_2SO_4. The organic phase was washed sequentially with 2 N H_2SO_4 and brine, and then dried (Na_2SO_4). Removal of the solvent gave a deep orange oil, which was purified by gravity column chromatography on silica gel (50 g). Fraction eluted with petroleum ether/EtOAc (6:4) gave a reddish oil, while fractions eluted with petroleum ether/EtOAc (5:5) afforded **3a** (4.48 g, 90%) as a white powder. When the reaction was carried out at room temperature, the *seco*-taxane **3a** was contaminated with compound **13**, structurally elucidated as its 7,9-bis(triethylsilyl) derivative [TES-Cl (4 equiv.), imidazole (4 equiv.), CH_2Cl_2]. IR (KBr): $\tilde{\nu}$ = 3460, 1759, 1722, 1679, 1649, 1270, 1283, 1140, 1031, 719 cm^{-1}. ^1H NMR (C_6D_6): δ = 0.69 (q, J = 7.6 Hz, TES), 0.88 (q, J = 7.6 Hz, TES), 0.93 (s, 17-H/3), 1.09 (t, J = 7.6 Hz, TES), 1.11 (t, J = 7.6 Hz, TES), 1.34 (s, 16-H/3), 1.95 (m, 6b-H), 1.95 (s, 19-H/3), 2.02 (s, 18-H/3), 2.06 (s, OAc), 2.55 (br. m, 6b-H), 3.22 (br. m, 14a,b-H), 3.91 (br. m, 7a,b-H), 3.92 (m, 20b-H), 4.24 (d, J = 10 Hz, 3-H), 4.30 (m, 13-H), 4.37 (d, J = 7.4 Hz, 20a-H), 4.68 (br. d, J = 11.4 Hz, 5-H), 5.92 (d, J = 10 Hz, 2-H), 7.07 (C-Bz), 7.11 (BB′-Bz), 8.10 (AA′-Bz) ppm. ^{13}C NMR (C_6D_6): δ = 5.2 (TES-CH_2), 7.0 (TES-CH_2), 7.5 (TES-Me), 7.7 (TES-Me), 14.8 (C-18), 16.0 (C-19), 22.4 (OAc), 25.1 (C-17), 26.7 (C-16), 37.8 (C-14), 38.3 (C-6), 43.9 (C-15), 44.4 (C-3), 58.7 (C-7), 67.4 (C-13), 73.6 (C-2), 80.7 (C-20), 80.8 (C-4), 91.8 (C-1), 93.2 (C-5), 128.9 (Bz), 130.2 (Bz), 132.3 (C-8), 133.0 (Bz), 133.0 (Bz), 142.2 (C-12), 142.9 (C-11), 149.6 (C-9), 165.8 (Bz), 170.1 (OAc), 192.2 (C-10) ppm.

Synthesis of 14-Hydroxy-10-dehydro-7,8-*seco*-10-deacetylbaccatin III 1,14-Acetonide (12): $Cu(OAc)_2·H_2O$ (1.2 g) was added in small portions over ca. 5 min to a magnetically stirred suspension of **11**[20] (604 mg, 1 mmol) in methanol (10 mL). After stirring overnight, the reaction mixture was worked up by concentration and addition of water (60 mL) and EtOAc (60 mL). The organic phase was washed with 2 N NH_3 to remove copper salts, and then with brine. After drying (Na_2SO_4) and evaporation, the residue was taken up in methanol (5 mL) and treated with $CeCl_3·7H_2O$ (371 mg, 1 mmol, 1 mol equiv.) and next $NaBH_4$ (60 mg). After stirring 20 min at room temp., the reaction mixture was worked up by the addition of satd. NH_4Cl (30 mL) and extraction with EtOAc (3 × 20 mL). The organic phase was washed with brine and dried (Na_2SO_4), and the solvents were evaporated. The residue was purified by column chromatography on silica gel (25 g), with use of a petroleum ether/EtOAc gradient. Fractions eluted with petroleum ether/EtOAc (3:7) gave a complex mixture of taxanes that was not further characterized, while fractions eluted with petroleum ether/EtOAc (1:9) afforded **12** (124 mg, 21% from **11**) as a white powder. M.p. 109−112 °C. IR (KBr): $\tilde{\nu}$ = 3432, 1736, 1649, 1269, 1159, 1092, 1026, 714 cm^{-1}. ^1H NMR ($CDCl_3$) Major rotamer: δ = 1.05 (s, acetonide), 1.11 (s, 17-H/3), 1.17 (s, 16-H/3), 1.43 (s, acetonide), 1.72 (s, OAc), 1.82 (br. s, 19-H/3), 2.02 (br. s, 18-H/3), 2.03 (br. m, 6b-H), 2.48 (br. m, 6a-H), 3.83 (br. m, 7b-H), 3.91 (br. m, 7a-H), 4.28 (d, J = 8.1 Hz, 20b-H), 4.35 (d, J = 7.5 Hz, 3-H), 4.84 (d, J = 2 Hz, 14-H), 4.98 (d, J = 2 Hz, 13-H), 5.18 (d, J = 8.1 Hz, 20a-H), 5.36 (br. d, J = 8.0 Hz, 5-H), 6.01 (d, J = 7.5 Hz, 2-H), 7.49 (BB′-Bz), 7.59 (C-Bz), 8.00 (AA′-Bz) ppm. Minor rotamer: δ = 1.03 (s, acetonide), 1.13 (s, 17-H/3), 1.13 (s, 16-H/3), 1.39 (s, acetonide), 1.92 (br. s, 18-H/3), 2.00 (br. m, 6b-H and 6a-H), 2.35 (s, OAc),), 2.44 (br. s, 19-H/3), 3.14 (br. m, 7b-H and 7a-H), 4.29 (d, J = 2 Hz, 14-H), 4.36 (d, J = 8.1 Hz, 20b-H), 4.42 (d, J = 8.1 Hz, 20a-H), 4.86 (d, J = 7.5 Hz, 3-H), 4.85 (d, J = 2 Hz, 13-H), 4.99 (br. d, J = 8.0 Hz, 5-H), 5.98 (d, J = 7.5 Hz, 2-H), 7.49 (BB′-Bz), 7.62 (C-Bz), 8.16 (AA′-Bz) ppm. ^{13}C NMR ($CDCl_3$): Major rotamer: δ = 14.3 (C-19), 14.7 (C-18), 22.0 (OAc), 22.2 (C-16), 26.8 (C-17), 38.1 (C-6), 42.7 (C-15), 44.5 (C-3), 59.0 (C-7), 63.7 (C-2), 73.4 (C-13), 74.9 (C-20), 90.3 (C-1), 83.5 (C-14), 86.3 (C-4), 86.4 (C-5), 125.0 (C-8), 129.0 (Bz), 129.1 (Bz), 129.5 (Bz), 133.6 (Bz), 137.5 (C-12), 142.5 (C-11), 148.9 (C-9), 165.5 (Bz), 169.1 (OAc), 191.3 (C-10) ppm. Minor rotamer: δ = 13.6 (C-19), 14.3 (C-18), 22.5 (OAc), 21.4 (C-16), 27.2 (C-17), 34.0 (C-6), 42.1 (C-3), 43.2 (C-15), 60.3 (C-7), 69.9 (C-2), 74.7 (C-13), 76.5 (C-20), 89.1 (C-1), 84.1 (C-14), 85.8 (C-4), 85.8 (C-5), 125.0 (C-8), 128.7 (Bz), 129.8 (Bz), 129.9 (Bz), 133.6 (Bz), 138.6 (C-12), 142.5 (C-11), 148.8 (C-9), 165.6 (Bz), 170.0 (OAc), 191.4 (C-10) ppm. HRMS (70 eV): m/z = 600.2588 (calcd. for $C_{32}H_{40}O_{11}$, 600.2571).

Synthesis of 10-Dehydro-7,8-*seco*-10-deacetylcephalomannine (15). a. Chemoselective Deacetylation and Silylation of Cephalomannine (14a): H_2O_2 (30%, 100 mL) and $NaHCO_3$ (20 g) were added to a solution of cephalomannine (**14a**, 2.0 g, 2.40 mmol) in THF (200 mL). After stirring at room temperature for 24 h, the reaction mixture was worked up by dilution with EtOAc and washed with 5% $Na_2S_2O_3$ and then with brine. After drying (Na_2SO_4) and evaporation, the residue was dissolved in petroleum ether/EtOAc (5:5) and purified by column chromatography (30 g silica gel, petroleum ether/EtOAc, 5:5, as eluent) to give 10-deacetylcephalomannine (**14b**, 1.67 g, 88%) as a white, fluffy powder.[32] This was dissolved in dry DMF (20 mL) and treated sequentially with imidazole (573 mg, 8.42 mmol, 4 mol equiv.) and TES-Cl (1.42 mL, 8.42 mmol, 4 mol equiv.). After stirring at room temperature for 1 h , the reaction mixture was worked up by pouring into a stirred suspension of Celite (3.2 g) in water (80 mL) and filtration through a sintered glass. The cake was washed with water to remove most of the DMF and next with EtOAc to recover the silylated product. After washing with brine, drying (Na_2SO_4) and evaporation, the residue was purified by column chromatography on silica gel to afford **14c** (967 mg, 51%) as a white powder, m.p. 111 °C. IR (KBr): $\tilde{\nu}$ = 3493, 1752, 1724, 1716, 1680, 1375, 1271, 1244, 1138, 984 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.59 (q, J = 7.9 Hz, OTES), 0.99 (t, J = 7.9 Hz, OTES), 1.14 (s, 17-H/3), 1.21 (s, 16-H/3), 1.68 (s, 19-H/3), 1.71 (br. s, Tigl),), 1.79 (br. s, Tigl + 18-H/3), 2.35 (br. s, Ac), 3.90 (d, J = 7.5 Hz, 3-H), 4.19 (d, J = 9 Hz, 20b-H), 4.31 (dd, J = 11, 7 Hz, 7-H), 4.32 (d, J = 9 Hz, 20b-H), 4.70 (d, J = 3 Hz, 2′-H), 4.95 (br. d, J = 7.5 Hz, 5-H), 5.18 (s, 10-H), 5.60 (dd, J = 9, 3 Hz, 3′-H), 5.69 (d, J = 7.5 Hz, 2-H), 6.19 (br. t, J = 7.5 Hz, 13-H), 6.44 (br. q, J = 7 Hz, Tigl), 6.65 (br. d, J = 9 Hz, NH), 7.40 (m, Ph), 7.52 (BB′-Bz), 7.65 (C-Bz), 8.11 (AA′-Bz) ppm.

b. Autoxidation, Reductive Fragmentation and Desilylation of 14c: $Cu(OAc)_2·H_2O$ (10 g) was added to a solution of **14c** (904 mg, 1.07 mmol) in methanol (20 mL), and the suspension was magnetically stirred for 24 h in a flask open to the air. The reaction mixture was worked up by concentration under reduced pressure, filtration through Celite and washing of the cake with EtOAc. The organic phase was washed with 2% NH_3 and brine and dried (Na_2SO_4).

Removal of the solvent left a pale bluish powder, which was purified from copper impurities by filtration through silica gel, providing **14d** (860 mg, 89%) as an off-white powder (ca. 4:1 mixture of 7α-hydroxy and 7β-hydroxy epimers). ^{1}H NMR spectroscopic data ($CDCl_3$) of the major epimer, which could be purified after desilylation: ^{1}H NMR: δ = 1.14 (s, 16-H/3), 1.25 (s, 17-H/3), 1.74 (s, 19-H/3), 1.71 (br. s, Tigl),), 1.79 (br. s, Tigl + 18-H/3), 2.52 (br. s, Ac), 3.87 (br. d, *J* = 10 Hz, 7-H), 4.03 (d, *J* = 7.5 Hz, 3-H), 4.36 (d, *J* = 9 Hz, 20b-H), 4.42 (d, *J* = 10 Hz, OH), 4.54 (d, *J* = 9 Hz, 20b-H), 4.72 (d, *J* = 3 Hz, 2′-H), 4.95 (m, 5-H), 5.62(dd, *J* = 9, 3 Hz, 3′-H), 5.89 (d, *J* = 7.5 Hz, 2-H), 6.19 (br. t, *J* = 7.5 Hz, 13-H), 6.44 (br. q, *J* = 7 Hz, Tigl), 6.53 (br. d, *J* = 9 Hz, NH), 7.40 (m, Ph), 7.53 (BB′-Bz), 7.66 (C-Bz), 8.11 (AA′-Bz) ppm.

This was directly employed for the reductive fragmentation. To this end, a solution of **14d** (860 mg, 0.95 mmol) was dissolved in dry THF (ca. 10 mL). After this mixture had been cooled to −15 °C, a solution of ^{l}-selectride (1.0 M, 2.86 mL, 2.86 mmol, 3 mol equiv.) was added dropwise. At the end of the addition, the yellow solution was worked up by dilution with EtOAc and the addition of 2 N H_2SO_4. After washing with brine and evaporation, the residue of the organic phase was dissolved in methanol (10 mL) and treated with 2 mL of a solution of acetyl chloride in methanol (560 μL in 10 mL). After stirring at room temperature for 15 min, the reaction mixture was diluted with EtOAc and washed with satd. $NaHCO_3$ and brine. After drying (Na_2SO_4) and evaporation, the residue was purified by column chromatography on silica gel (25 mL, petroleum ether/EtOAc, 5:5, as eluent) to afford **15** (355 mg, 47% from **14d**).

10-Dehydro-7,8-*seco*-10-deacetylcephalomannine (15): White powder, m.p. 150 °C. IR (KBr): ν̃ = 3418, 1740, 1653, 1636, 1273, 1107, 1069, 99, 712 cm^{-1}. ^{1}H NMR ($CDCl_3$, 40 °C): δ = 1.20 (s, 16-H/3), 1.40 (s, 17-H/3), 1.60 (br. s, 18-H/3 + Tigl), 1.80 (br. s, Tigl), 1.92 (br. s, 19-H/3), 2.06 (br. s, OAc), 3.90 (br. m, 7b-H), 4.20 (br. m, 7a-H), 4.28 (d, *J* = 7.5 Hz, 3-H), 4.30 (m, 20a,b-H), 4.80 (m, 2′-H), 5.15 (br. d, *J* = 8.0 Hz, 5-H), 5.60 (d, *J* = 7.5 Hz, 2-H), 5.70 (dd, *J* = 8, 2 Hz, 3′-H), 6.17 (br. t, *J* = 6 Hz, 13-H), 6.36 (br. q, *J* = 7 Hz, Tigl), 6.30 (br. s, OH), 6.64 (d, *J* = 9 Hz, NH), 7.20−7.36 (m, Ph), 7.42 (BB′-Bz), 7.52 (C-Bz), 8.04 (AA′-Bz) ppm. HRMS (70 eV): *m*/*z* = 789.3370 (calcd. for $C_{43}H_{54}NO_{13}$, 789.3360).

Reduction of 13-TES-10-deacetyl-10-dehydro-11(15→1)abeobaccatin V (8) with $NaBH_4$/$CeCl_3$: $CeCl_3 \cdot 7H_2O$ (58 mg, 0.16 mmol, 1 mol equiv.) was added to a solution of **8** (100 mg, 0.16 mmol) in MeOH (10 mL). After the mixture had been stirred at room temperature for 5 min, $NaBH_4$ (10 mg) was added. After 10 min the reaction mixture was worked up by dilution with EtOAc and brine. The organic phase was washed with brine and dried (Na_2SO_4), and the solvents were evaporated. The residue was purified by column chromatography on silica gel (2.5 g, petroleum ether/EtOAc, 5:5, as eluent), affording **16** (98 mg, 98 %).

13-TES-9-dihyhdro-10-deacetyl-10-epi-11(15→1)abeobaccatin V (16): Foam. IR (KBr): ν̃ = 3850, 1719, 1630, 1458, 1273, 1096, 1069, 712 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.64 (q, *J* = 7.6 Hz, TES), 1.01 (t, *J* = 7.6 Hz, TES), 1.61 (s, 19-H/3), 1.69 (s, 17-H/3), 1.76 (m, 14a-H), 1.98 (s, 18-H/3), 2.29 (s, Ac), 2.29 (m, 14a-H), 2.32 (m, 6a-H), 2.39 (m, 6b-H), 3.22 (m, 3-H), 3.70 (m, 9-H), 4.13 (m, 7 H), 4.27 (d, *J* = 8.4 Hz, 20a-H), 4.40 (m, 10-H), 4.52 (m, 13-H), 4.52 (d, *J* = 8.4 Hz, 20b-H), 4.75 (br. s, 16a-H), 4.83 (br. s, 16b-H), 5.02 (dd, *J* = 8.4, 2.7 Hz, 5-H), 5.89 (d, *J* = 8.0 Hz, 2-H), 7.48 (BB′-Bz), 7.62 (C-Bz), 8.04 (AA′-Bz) ppm. ^{13}C NMR ($CDCl_3$): δ = 4.9 (TES-CH_2), 6.8 (TES-Me), 13.0 (C-18), 18.0 (C-19), 21.0 (C-17), 21.8 (Ac), 35.9 (C-6), 38.3 (C-3), 42.4 (C-14), 62.1 (C-1), 70.4 (C-2), 71.0 (C-10), 74.4 (C-13), 76.0 (C-20), 81.2 (C-4), 83.4 (C-5), 112.2 (C-16), 128.6 (Bz), 129.7 (Bz), 129.9 (Bz), 133.5 (Bz), 135.9 (C-11), 143.6 (C-12), 145.5 (C-15), 165.6 (Bz), 172.0 (OAc) ppm. The signals of C-7, C-8 and C-9 could not be detected. HRMS (70 eV): *m*/*z* = 642.3229 (calcd. for $C_{35}H_{50}O_9Si$, 642.3224).

Treatment of **16** with dimethoxypropane and *p*-toluenesulfonic acid afforded **17a/b** (45%). NMR spectroscopic data for the major isomer (**17a**) were: ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 19-H/3), 1.50 (acetonide methyls), 1.80 (s, 17-H/3), 2.05 (m, 14a-H), 1.98 (s, 18-H/3), 2.18 (m, 6a-H), 2.19 (m, 14a-H), 2.27 (s, Ac), 2.43 (m, 6b-H), 3.18 (d, *J* = 8.2 Hz, 3-H), 3.34 (s,. OMe), 3.83 (d, *J* = 7 Hz,, 9-H), 3.91 (m, 7 H), 4.05 (d, *J* = 7.4 Hz, 13-H), 4.09 (d, *J* = 8.0 Hz, 20a-H), 4.48 (d, *J* = 7 Hz, 10-H), 4.68 (d, *J* = 8.0 Hz, 20a-H), 4.79 (s, 16a-H), 4.90 (s, 16b-H), 4.92 (m, 5-H), 5.78 (d, *J* = 8.2 Hz, 2-H), 7.48 (BB′-Bz), 7.60 (C-Bz), 8.05 (AA′-Bz) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.8 (C-18), 18.5 (C-19), 21.5 (C-17), 22.3 (Ac), 29.2 (acetonide methyls), 32.9 (C-6), 33.5 (C-14) 36.4 (C-3), 37.3 (C-8), 57.3 (OMe), 62.6 (C-1), 69.2 (C-10), 72.6 (C-2), 73.8 (C-7), 78.6 (C-20), 80.9 (C-9), 82.6 (C-5), 84.3 (C-4), 89.1 (C-13), 99.7 (acetonide), 112.7 (C-16), 128.6 (Bz), 129.8 (Bz), 130.1 (Bz), 133.3 (Bz), 137.3 (C-11), 141.9 (C-12), 147.2 (C-15), 165.9 (Bz), 168.9 (OAc) ppm.

Reduction of 13-TES-10-deacetyl-10-dehydro-11(15→1)abeobaccatin V (8) with L-Selectride: L-Selectride (1 M in THF, 312 μL, 0.31 mmol, 2 mol equiv.) was added dropwise to a cooled (−78 °C) solution of **8** (100 mg, 0.16 mmol) in dry THF. After 5 min, the yellow/orange reaction mixture was worked up by dilution with EtOAc and treatment wit 2 N H_2SO_4. The organic phase was sequentially washed with 2 N H_2SO_4 and brine, and then dried (Na_2SO_4). Removal of the solvent gave a deep orange oil, which was purified by gravity column chromatography on silica gel (2.5 g, petroleum ether/EtOAc, 8:2, as eluent) to give **18** (18 mg, 18%) as a foam, IR (KBr): ν̃ = 3400, 1780, 1721, 1273, 1100, 1067, 1048 cm^{-1}. ^{1}H NMR (C_6D_6): δ = 0.63 (q, *J* = 7.6 Hz, TES), 1.00 (s, OAc), 1.02 (t, *J* = 7.6 Hz, TES), 1.56 (s, 19-H/3), 1.95 (s, 17-H/3), 2.12 (m. 6a-H), 2.15 (m, 14a-H), 2.43 (s, 18-H/3), 2.45 (m, 3-H), 2.47 (m, 14b-H), 2.64 (dd, *J* = 5.9, 17.1 Hz, 6b-H), 4.59 (m, 13-H), 4.59 (m, 7-H), 4.75 (d, *J* = 5.9 Hz, 5-H), 4.67 (d, *J* = 8.1 Hz, 20a-H), 4.75 (br. d, *J* = 5.9 Hz, 5-H), 4.80 (m, 20a-H), 4.80 (s, 16a-H), 5.01 (s, 16b-H), 6.17 (d, *J* = 10 Hz, 2-H), 7.03 (C-Bz), 7.12 (BB′-Bz), 7.93 (AA′-Bz) ppm. ^{13}C NMR (C_6D_6): δ = 5.6 (TES-CH_2), 7.4 (TES-Me), 11.7 (C-19), 15.4 (C-18), 20.6 (OAc), 21.0 (C-17), 30.6 (C-6), 38.9 (C-3), 44.4 (C-14), 47.1 (C-8), 59.6 (C-1), 70.4 (C-2), 74.4 (C-20), 78.4 (C-7), 78.5 (C-13), 79.1 (C-9), 79.3 (C-4), 83.6 (C-5), 113.8 (C-16), 129.0 (Bz), 130.4 (Bz), 130.8 (Bz), 132.7 (C-11), 133.5 (Bz), 148.9 (C-15), 151.3 (C-12), 165.3 (Bz), 168.8 (OAc) ppm. HRMS (70 eV): *m*/*z* = 638.2928 (calcd. for $C_{36}H_{48}O_{10}Si - H_2O$, 638.2911).

Acknowledgments

We are grateful to Dr. Jasmin Jakupovic (AnalytiCon Discovery GmbH, Potsdam, Germany) for his useful suggestions and encouragement throughout this work.

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Received June 26, 2003

