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AN ENANTIOSPECIFIC SYNTHESIS OF A TAXOL A-RING BUILDING UNIT.

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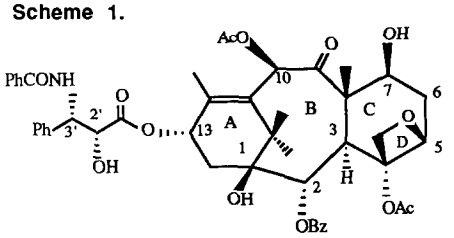
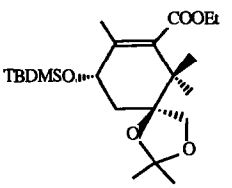
Abstract. The optically active Taxol A-ring segment **2** was synthesized from L-arabinose via ring closure of epoxy-allylsilane **3** with $BF_3.OEt_2$.

The chemistry of the taxane diterpenoids has attracted considerable interest during the last few years. Several syntheses of the taxane skeleton or subunits thereof have been reported since 1978.[1,2] One major reason for the interest in the taxanes is the discovery that Taxol (**1**), which was isolated from yew trees (*Taxus baccata* among others), possessed anti-leukemic and anti-tumor properties,[3] and is now undergoing clinical testing in the USA and France. Very recently, interest has been directed towards the possibility of preparing modified Taxol derivatives or Taxol by starting from Taxol[4] or Bacchatin III[5].

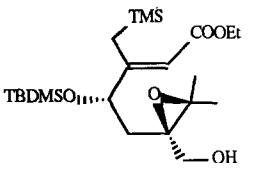
Scheme 1.



1
TAXOL



2



3

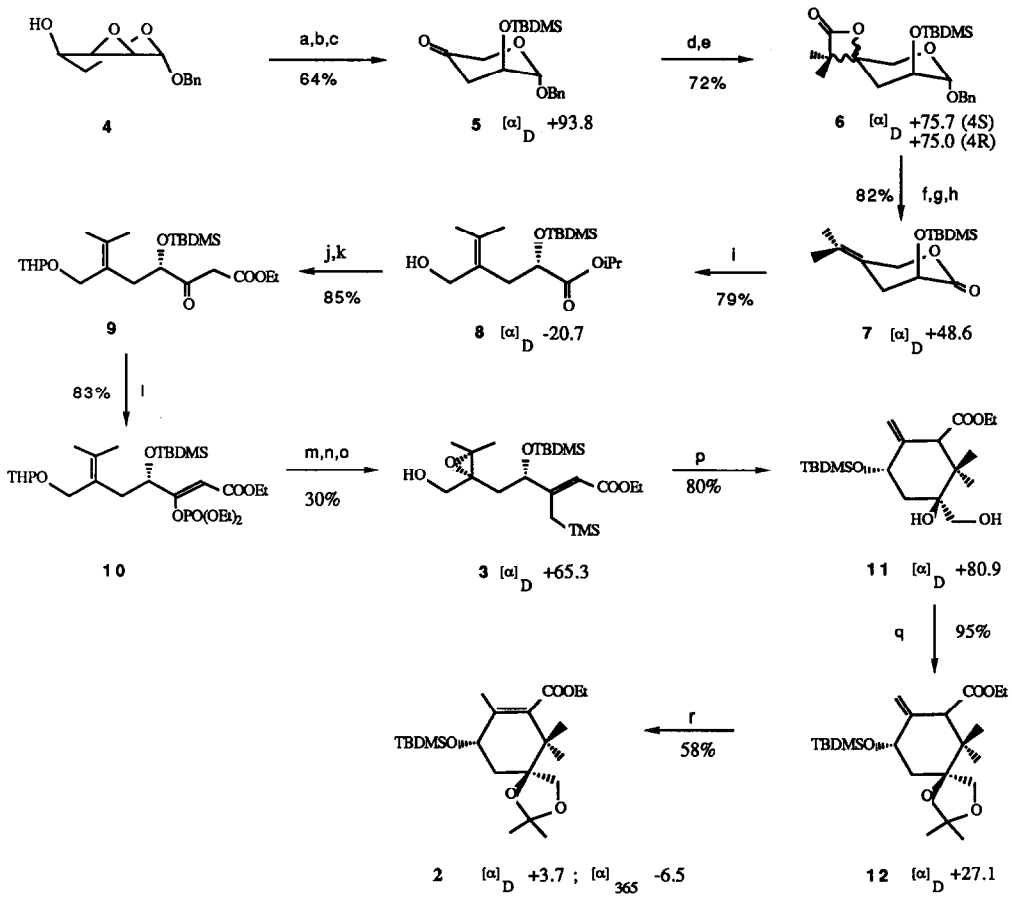
We now report the enantiospecific synthesis of the Taxol A-ring derivative **2** equipped with functionalities suitable for further elaboration of the B,C,D-ring system. A similar compound that lacks the tertiary alcohol function at position 1 (taxane numbering) was synthesized from D-camphor.[6] Our synthetic scheme is based on an electrophilic polyene cyclization.[7] Several years ago it was shown that allylsilanes were particularly suitable for this type of cyclization,[8] and the concept has recently been developed by Weiler and coworkers[9] to also include epoxy-allylsilanes.[10] This led us to regard optically active **3** as a suitable precursor for Lewis acid mediated ring closure for the production of the Taxol A-ring system.

The synthesis of **3** from L-arabinose is outlined in Scheme 2. The choice of arabinose as starting material, in spite of the fact that only the original C-2 asymmetric center was retained, was justified since there existed an efficient 5-step literature procedure for the synthesis of the epoxy alcohol **4**.[11] Furthermore, arabinose is rather inexpensive and available in both the D- and the L-forms.

The epoxy alcohol **4** was oxidized by the Swern procedure[12] to give the corresponding epoxy ketone, and the epoxide ring was opened with NaI[13] to give the keto-alcohol derivative **5**, after protection of the hydroxyl group with TBDMS-Cl. Transformation of **5** into the isopropylidene derivative **7** was made by a multistep sequence: the ketone **5** was treated with the bis-anion of isobutyric acid, followed by benzenesulfonyl chloride,[14] to give a C-4

epimeric mixture of the spiro β-lactones **6**. The benzyl group was removed by hydrogenolysis and the resulting hemiacetal was oxidized with PDC[15] to give the corresponding bis-spirolactone, still an epimeric mixture at C-4. Thermolysis of this material afforded the olefin **7**. Even though this sequence seems rather lengthy it has the advantage of keeping the olefin protected during hydrogenolysis of the benzyl group. The yield in each separate step (**5** ->**7**) was 85-93%. Lactone **7** was opened with $Ti(OiPr)_4$ to give the allylic alcohol **8**, which was protected with dihydropyran. Subsequent treatment of the protected allylic alcohol with $LiCH_2COOEt$ (generated from ethyl acetate and $(TMS)_2NLi$) gave the β-ketoester **9**.

Scheme 2.[17]



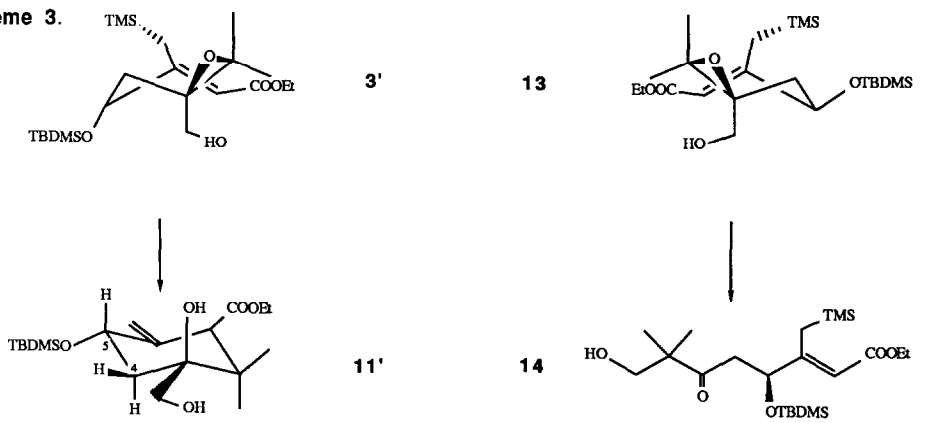
a) DMSO,$(COCl)_2$, NEt_3; b) NaI, acetone, HOAc, NaOAc; c)TBDMS-Cl, imidazol; d) LDA, isobutyric acid; e) $PhSO_2Cl$, pyr; f) Pd-C, H_2, HOAc; g) PDC, Ac_2O, CH_2Cl_2; h) 170° C; i) $Ti(OiPr)_4$; j) DHP, Pyridinium tosylate; k) $(TMS)_2NLi$, TMEDA, EtOAc; l) KOtBu, $ClPO(OEt)_2$; m) $TMSCH_2MgCl$, 5% $Ni(acac)_2$; n) Pyridinium tosylate, iPrOH, 50°C; o) $Ti(OiPr)_4$, (-)-DET, TBHP, -25°C; p) $BF_3.OEt_2$, CH_2Cl_2, 0°C,15 min; q) $BF_3.OEt_2$, acetone, CH_2Cl_2; r) DBU, 185 °C, 1h.

The trimethylsilylmethyl group was introduced by treating the phosphoenolate **10** with $TMS\text{-}CH_2MgCl$ and a catalytic amount of $Ni(acac)_2$.[9] Removal of the THP-protecting group followed by the Sharpless asymmetric

epoxidation reaction[16] gave **3** (90-95% d.e.). The choice of (-)-DET in the epoxidation reaction ensures that the asymmetric epoxide carbon will have the (R)-configuration, as is required in Taxol. Treatment of **3** with $BF_3.OEt_2$ at 0 °C gave the six-membered ring compound **11**, which easily formed the corresponding acetonide **12** with acetone in the presence of $BF_3.OEt_2$ in CH_2Cl_2. The reactions with $BF_3.OEt_2$ had to be monitored carefully with TLC in order to avoid removal of the TBDMS protecting group. This seems to be the only example of a "polyene-type" cyclization of an epoxy-olefin where the epoxide is tetrasubstituted.

The epoxide **13** (Scheme 3), obtained by replacing (-)-DET with (+)-DET in the Sharpless asymmetric epoxidation, did not undergo the cyclization with $BF_3.OEt_2$. Instead the hydroxymethyl group migrated to give the ketone **14**. Inspection of the tentative chair transition state arrangements **3'** and **13** for the two cases does not reveal any obvious reason why **3** cyclized and **13** did not.[18] The quasi axial orientation of the TBDMSO-group in **3'** could even counteract this transition state. Moreover, four large groups are placed in axial or quasi axial positions in **3'** while in **13** there are only three similarly placed large groups. The best orientation of the C-$SiMe_3$ bond for cyclization should be perpendicular to the plane of the double bond in order to maximize the overlap between the σ–orbital of the C-$SiMe_3$ bond and the π-orbitals. A space filling model of **13** indicates that the TBDMS group may force the TMS group out of this orientation making cyclization less favourable. However, coordination of the Lewis acid must also be included in the transition state and it is well known that BF_3 forms complexes with alcohols, ethers and carbonyl groups.[19] Thus **3** and **13** may form complexes with up to 3 molecules of BF_3 in unknown spacial arrangements.[20] Consquently, further discussion of the mechanism of ring closure must wait until more details are available.

Scheme 3.



Only one stereoisomer of **11** was formed in the cyclization of **3**. According to ^{1}H-NMR analysis it should have the chair form as shown in **11'** since the coupling constants ($J_{4,5}$ = 11.7 and 5.1 Hz) indicate one *trans* diaxial and one axial-equatorial (gauche) relationship. Thus, the initial conformation of **11** (similar to the transition state; c.f.**3'**) was transformed into the final conformation **11'**. The stereostructure at C-1 could not be determined from the ^{1}H-NMR spectra of **11** and **12**. However, this is not important because in the final product (**2**), C-1 has been converted into a sp^2 carbon.

The isomerization of **12** into **2** caused considerable difficulties. Having tried a large number of isomerization conditions, we found that heating **12** in neat DBU at 185 °C for 1 h resulted in an acceptable yield of **2** (58%). The present work constitutes the first enantiospecific synthesis of the Taxol A-ring system; a full account will be reported shortly. The use of **11**,**12** and **2** for the synthesis of optically active taxanes is now under investigation.

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17. All new substances had correct elemental compositions and NMR data (^{1}H,^{13}C, including 2D HOMCOR and HETCOR recorded on a Varian XL-300 NMR spectrometer). Specific rotations were measured at 22 °C (c 0.3-2.6, $CHCl_3$), except where otherwise indicated.
(**2**, $CDCl_3$), ^{1}H δ: 0.09 (s,6H, -Si(CH_3)$_2$-), 0.90 (s,9H, -SiC($\underline{CH}_3$)$_3$), 1.08 (s, 3H, CH_3-6), 1.17 (s, 3H, CH_3-6), 1.32 (t, 3H, CO_2CH_2-$\underline{CH}_3$, J 7.0 Hz), 1.36 (q,3H, acetal-CH_3, J 0.6 Hz), 1.46 (q, 3H, acetal-CH_3, J 0.6 Hz), 1.70 (d, 3H, CH_3-2, J 1.0 Hz), 1.89 (dd, 1H, H-4, J 13.2 and 8.3 Hz), 2.22 (dd, 1H, H-4, J 13.2 and 5.8 Hz), 3.76 (d, 1H, acetal-CH_2-, J 8.7 Hz), 3.93 (d, 1H, acetal-CH_2-, J 8.7), 4.34 (ddq, 1H, H-3, J 8.3, 5.8 and 1.0 Hz), 4.24 (q, 2H, CO_2-$\underline{CH}_2$-, J 7.0 Hz); ^{13}C δ: -4.84, -4.20, 14.30, 17.09, 18.03, 21.56, 24.89, 25.82, 26.26, 28.07, 38.88, 38.90, 60.36, 68.68, 69.76, 84.78, 109.58, 135.04, 135.52, 169.76.
(**11**, $CDCl_3$), ^{1}H δ: 0.08 (2s, 6H, -Si(CH_3)$_2$-), 0.92 (s, 9H, -SiC(CH_3)$_3$), 0.97 (s, 3H, CH_3-2), 1.11 (s, 3H, CH_3-2), 1.27 (t, 3H, -CO_2CH_2-$\underline{CH}_3$, J 7.0 Hz), 1.61 (dd, 1H,H-4, J 13.2 and 11.7 Hz), 2.18 (dd, 1H, H-4, J 13.2 and 5.1 Hz), 2.38 (dd, 1H, -CH_2-$\underline{OH}$, J 8.3 and 3.7 Hz), 3.17 (s, 1H, H-1), 3.33 (dd, 1H, -$\underline{CH}_2$-OH, J 11.0 and 8.3 Hz), 3.64 (dd, 1H, -$\underline{CH}_2$-OH, J 11.0 and 3.7 Hz), 4.16 and 4.17 (dq, 1H,-CO_2-CH_2-, J 10.5 and 7.0 Hz), 4.63 (dddd, 1H, H-5, J 11.7, 5.1, 2.0 and 2.0 Hz), 5.00 and 5.28 (dd, 1H, C-H, J 2.0 and 2.0 Hz), 5.72 (s, 1H, OH); ^{13}C δ: -4.95, 14.10, 18.51, 21.24, 25.53, 25.96, 42.39, 61.91, 64.12, 67.05, 67.32, 75.88, 111.96, 144.10, 175.89.
18. We anticipate that the transition state arrangements are similar to the one discussed by Armstrong and Weiler in Ref 10, i.e. the tertiary hydroxyl and the ester groups will become *cis* oriented in the product.
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