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New Synthesis of a Taxol A-Ring System.

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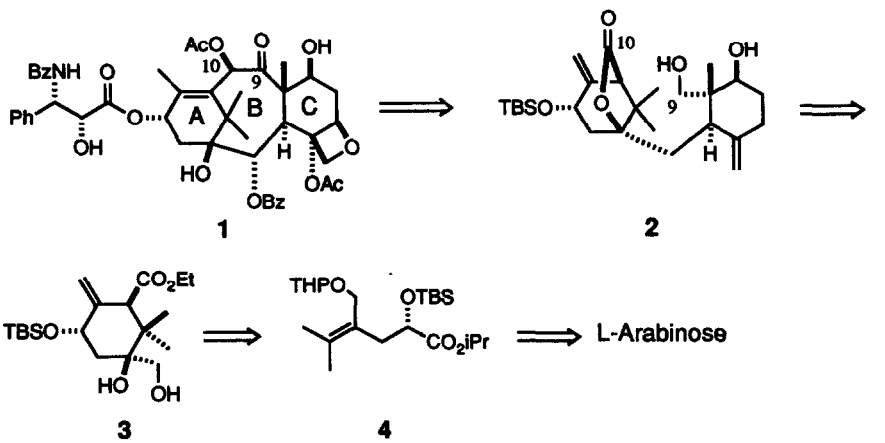
Abstract. The optically active taxol A-ring unit **3** was synthesized in 11 steps from 2-isopropyl-2-propenol. The stereogenic centers were introduced via the asymmetric glyoxylate-ene reaction and the Sharpless asymmetric epoxidation reaction.

The total synthesis of taxol (**1**) and analogous compounds has attracted an increasing interest due to their manifested anticancer effect.[1-5] We reported earlier that the enantiomerically pure taxol A-ring unit **3** could be synthesized from L-arabinose (Scheme 1).[6,7]



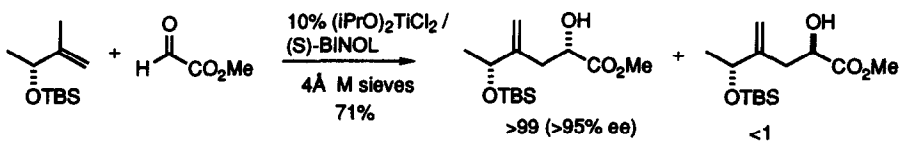
Scheme 1

The reaction sequence was too long, however, in order to be practically useful for further development of the taxol synthesis, although we used the small amount of material available to prepare *seco*-taxane **2**[8]. This compound has all the carbon atoms required for the taxol carbon skeleton and also many of the stereogenic centers and functionalities which makes it an interesting intermediate for further transformations; in particu-

lar the C9-C10 bond formation. Obviously, larger amounts of **2** is needed and we now report a new and shortened synthetic route to **3**, which will allow the preparation of multigram quantities of **2** or similar compounds. Other workers have synthesized optically active A-ring units similar to **3**.[5,9,10]

RESULTS AND DISCUSSION

Compound **4** was synthesized in 15 steps and used as an intermediate in our previous route to **3**.[6,7] A more elegant synthesis of **4** and similar structures would be to apply the catalytic asymmetric glyoxylate-ene reaction as recently described by Mikami et al.[11-13] These authors used a Lewis acid system composed of $Cl_2Ti(OiPr)_2$ (or the corresponding bromide) and optically active 2,2´-dihydroxy-1,1´-binaphthyl (BINOL) to control the stereoselectivity e.g. in the ene reaction between methyl glyoxylate and allylic silyl ethers as exemplified in Scheme 2. In addition to the high de and ee a perfect regio control was achieved; only the allylic ethers and no enol ethers were formed.



Scheme 2[12]

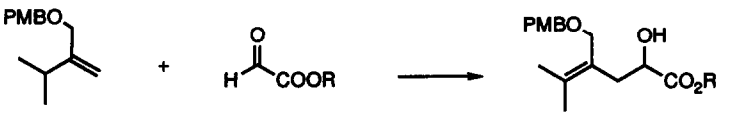
Unfortunately, these reaction conditions applied on **5**[14] and ethyl glyoxylate gave only traces of the ene product (Table, Entry 3). Attempts with other Lewis acids such as $TiCl_4$, $SnCl_4$, Et_2AlCl, $BF_3 \cdot OEt_2$ and $AlMe_3$/(S)-BINOL[15] in catalytic (0.05-0.1 mol%) and stoichiometric amounts were unsuccessful as well. Interestingly, despite that only traces of ene product was produced using a catalytic amount of $Cl_2Ti(OiPr)_2$, up to 80% yield of the expected ene product was obtained in experiments performed with 2 equiv of the Lewis acid and 5 equiv of ethyl glyoxylate (Entries 1, 2). But still only traces of the ene product was obtained using the chiral Lewis acid $Cl_2Ti(OiPr)_2$ / (S)-BINOL at the 2 equivalents level (Entry 3). It is not evident why compound **5** does not behave well in this type of reactions but a similar non-reactivity of the benzyl ether of 2-buten-1-ol has been noted.[13] A satisfactory explanation must await further investigation.

We next turned to ene reactions with chiral glyoxylates. Achmatowicz et al.[16] showed that it was possible to induce some optical activity (5-30% ee) in the product formed in the ene reaction between menthyl glyoxylates and 1-pentene using various Lewis acids. More recently Whitesell et al.[17-20] improved this type of re-

action considerably by using optically active *trans*-2-phenylcyclohexyl or 8-phenylmenthyl glyoxylate and tin(IV)chloride. As seen in the Table (Entries 4-6) these glyoxylates gave high yields of the ene products also in the case of **5**, and in particular both the regio- and stereoselectivity were preparatively useful by applying (-) -8-phenylmenthyl glyoxylate and tin(IV)chloride (Entry 6).

Attempted chain elongation using $LiCH_2COOEt$ did not work directly on the sterically hindered 8-phenylmenthyl ester (2S)-**11**. Instead, (2S)-**11** was hydrolysed (the chiral auxilliary was recovered in good yield) and the hydroxy acid formed was reesterified and protected to give the TBS protected ester **12** in 64 % overall yield (Scheme 3).

Table. The ene reaction between **5** and glyoxylates.



5

6; R = Et
7; R = trans-2-phenylcyclohexyl
8; R = (-)-8-phenylmenthyl

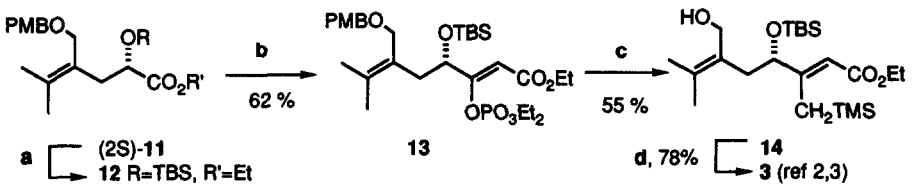
9
10
11

Entry	Glyoxylate	Catalyst	Product (% yield)	Diastereomeric ratio[c]
1	**6** (1 equiv)[a]	$Cl_2Ti(OiPr)_2$ (0.05 equiv)	**9** (trace)	—
2	**6** (5 equiv)[a]	$Cl_2Ti(OiPr)_2$ (2 equiv)	**9** (50-80)	—
3	**6** (1-5 equiv)[a]	$Cl_2Ti(OiPr)_2$ / (S)-BINOL (0.05-2 equiv)	**9** (trace)	—
4	**7** (1 equiv)	$Cl_2Ti(OiPr)_2$ (2 equiv)	**10** (90)	4.9:1
5	**7** (1 equiv)[b]	$SnCl_4$ (1 equiv)	**10** (>90)	6.4:1
6	**8** (1 equiv)[b]	$SnCl_4$ (1 equiv)	(2S)-**11** (>90)	>99:1

[a] 0.5 M with respect to **5** in CH_2Cl_2 at -20°C. [b] 0.15 M with respect to **5** in CH_2Cl_2 at -78°C. [c] See the Experimental part for the determination of the diastereomeric ratios.

Subsequent treatment with $LiCH_2COOEt$ gave the β-keto ester which was transformed into the enol phosphate **13** (Z:E 9:1). After purification the Z-isomer was coupled with $TMSCH_2MgCl$ / $Ni(acac)_2$ to give the corresponding allyl silane.[21] Oxidative cleavage of the PMB ether with DDQ gave the allylic alcohol **14**; some overoxidized product (aldehyde) was reduced to **14** by brief $CeCl_3/NaBH_4$ treatment during workup. Finally, compound **14** was converted into the taxol A-ring derivative **3** in two steps as reported earlier.[6,7] Since **3** was earlier prepared enatiomerically pure from L-arabinose its absolute configuration was known with a high degree of certainty. Thus, the ene reaction of **5** and (-)-8-phenylmenthyl glyoxylate produced (2S)-**11** as the major stereoisomer in agreement with the prediction from literature.[17,18,19,20]

The presented route allows the synthesis of considerable amounts of **3** and possibly other A-ring units in a few steps. We are continuing our work with *seco*-taxane **2** and similar derivatives for the development into taxanes.[8]



a. 1) NaOH; 2) DBU / EtBr; 3) TBSCl / imidazol. **b.** 1) LHMDS / TMEDA / EtOAc; 2) t-BuOK / $ClPO_3Et_2$. **c.** 1) $TMSCH_2MgCl$ / $Ni(acac)_2$; 2) DDQ. **d.** 1) t-BuOOH / $Ti(OiPr)_4$ / (-)-Diethyl tartrate; 2) $BF_3{\cdot}Et_2O$.

Scheme 3

EXPERIMENTAL

All liquid chromatography separations were performed using Merck SiO_2 60 (0.040-0.063 mm) silica gel. TLC analyses were done on Merck SiO_2 60 F_{254} precoated aluminum sheets and the spots were visualized with UV light or by charring with 5 % molybdatophosphoric acid in ethanol. NMR spectra were recorded at 23°C with a Varian XL-300 spectrometer operating at 300 MHz proton frequency (software version 6.2) using $CDCl_3$ as solvent and $CHCl_3$ as internal standard (δ 7.26 ppm as compared to TMS). Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Mass spectra were recorded on a Jeol JMS-SX 102. GC analyses were carried out on a Varian 3700 gas chromatograph equipped with a RSL-300 capillary

column at 130°C. Magnesium sulfate was used as drying reagent for organic extracts.

1-(4-Methoxybenzyloxy)-2-(2-propyl)-2-propene, (5). A solution of 2-(2-propyl)-2-propen-1-ol[22] (17.5 g, 0.175 mol) in THF (100 mL) was added slowly to a stirred suspension of NaH (57 % in mineral oil, 8.8 g, 0.19 mol) in DMF (100 mL) at 0°C under argon. The mixture was stirred for 30 min A solution of 4-methoxybenzyl chloride (25 mL, 0.18 mol) in THF (25 mL) was added slowly and the reaction mixture was stirred for 120 min[23] Water (10 mL) was added dropwise and the mixture was diluted with diethyl ether. The organic phase was washed with water and brine, dried and concentrated. Flash chromatography of the residue (heptane-EtOAc, 10:1) gave **5** (37.8 g, 98 %) as a clear oil. ^{1}H NMR δ 7.28 (d, 2 H, J 8.7 Hz), 6.89 (d, 2 H, J 8.7 Hz), 4.95, 5.04 (2 s, 2 H, 3-H), 4.43 (s, 2 H), 3.99 (s, 2 H), 3.81 (s, 3 H, OCH_3), 2.30-2.44 (m, 1 H), 1.07 (d, 6 H, J 6.9 Hz, CH_3). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.19; H, 9.12. Found: C, 76.38; H, 9.08.

Ethyl 2-hydroxy-4-[(4-methoxybenzyloxy)methyl]-5-methyl-4-hexenoate (9). Ethyl glyoxylate (**6**) (0.25 g, 2.50 mmol) and compound **5** (0.11 g, 0.50 mmol) were added to a solution of $Cl_2Ti(OiPr)_2$ (0.24 g, 1.00 mmol) in CH_2Cl_2 (1.0 ml) at -78 °C under argon. The reaction mixture was left for 48 h at -20 °C and was then diluted with diethyl ether and washed with saturated $NaHCO_3$ and brine, dried and concentrated. Flash chromatography of the residue (heptane-EtOAc) 3:1) gave **9** (0.12 g, 75%). ^{1}H NMR δ 7.28 (d, 2 H, J 8.7 Hz), 6.88 (d, 2 H, J 8.7 Hz), 4.47 (2 d, 2 H, J 11.3 Hz), 4.13-4.30 (m, 4 H), 3.92, 4.08 (2 d, 2 H, J 10.3 Hz), 3.80 (s, 3 H, OCH_3), 2.75 (2 m, 1 H, 3-H), 2.51 (dd, 1 H, J 9.0, 14.2 Hz, 3-H), 1.73, 1.75 (2 s, 6 H, CH_3), 1.29 (t, 3 H, J 7.0 Hz, $OCH_2\underline{CH_3}$). HRMS calcd for $C_{18}H_{27}O_5$ (M+1): 323.1858. Found: 323.1848.

***Trans*-2-phenylcyclohexyl 2-hydroxy-4-[(4-methoxybenzyloxy)methyl]-5-methyl-4-hexenoate, (10).** Method a) $SnCl_4$ (0.12 ml, 1.00 mmol) was added dropwise to a solution of racemic *trans*-2-phenylcyclohexyl glyoxylate (**7**) (0.23 g, 1.00 mmol) in CH_2Cl_2 (5 ml) at -78 °C under argon followed by compound **5** (0.26 g, 1.20 mmol) in CH_2Cl_2 (1 ml). The mixture was stirred for 10 min and was then diluted with diethyl ether, washed with saturated $NaHCO_3$ and brine, dried and concentrated. Flash chromatography of the residue (heptane-EtOAc, 3:1) gave crude **10** (416 mg, 92%). This alcohol decomposed on silica and could not be purified further. Instead the alcohol was protected as the somewhat more stable TBS-ether.

A solution of crude **10** (0.19 g, 0.30 mmol) imidazol (0.070 g, 0.80 mmol) and TBSCl (0.600 g, 0.40 mmol) in DMF (0.8 ml) was stirred over night. The reaction mixture was then diluted with diethylether, washed with 1M HCl, saturated $NaHCO_3$ and brine, dried and concentrated. Flash chromatography of the residue (heptane-EtOAc, 10:1) gave the slightly impure TBS ether of **10** (0.14 g, 83%). ^1H NMR δ 6.82-7.30 (m, 9H), 5.05 (m, 1H, 2-H), 4.31 (m, 2H), 3.78-4.02 (m, 3H), 3.81 (s, 3H, OCH_3), 2.67 (m, 1H), 1.25-2.25 (m, 10 H), 1.50, 1.63 (2s, 6H, CH_3), 0.79 (s, 9H, $SiC(CH_3)_3$), -0.12, -0.18 (2s, 6H, $Si(CH_3)_2$). Also this compound decomposed on silica, although more slowly than **10**, and could not be purified further. The diastereomeric ratio (dr) 6.4:1 was determined by ^{13}C NMR spectroscopy by comparing the height of the following signals from the major and minor diastereomers, respectively: δ major (minor) 69.5 (69.1), 35.4 (35.9), 34.2 (33.7).

Method b) The same procedure as for **9** was used, except that **7** was used instead of **6** and the reactants were used in 1:1:1 ratio, to give **10** (90%). The dr 4.9:1 was determined on the TBS ether by ^{13}C NMR spectroscopy as above.

In both these cases the dr:s reflect only the values of the chromatographed TBS ethers. The hydroxy esters were not stable enough to give reliable spectral data for the diastereomeric excess determination directly on the crude reaction products or after chromatography. Thus, the dr:s do not necessarily reflect the actual outcome of the respective reactions since the ratios of the stereoisomers may have been changed both in the decomposition itself and during the chromatographic procedures. Even if the diastereomers were not separated by TLC it is possible that minor amounts of one or both diastereomers inadvertently were removed in the chromatographic fractionation/pooling procedure.

Ethyl (2S)-2-[(t-butyldimethylsilyl)oxy]-4-[(4-methoxybenzyloxy)methyl]-5-methyl-4-hexenoate, (12). A solution of compound **5** (1.0 g, 4.5 mmol) in CH_2Cl_2 (1 mL) was added to a solution of (1R, 2S, 5R)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl glyoxylate (**8**)[19] (0.95 g, 3.3 mmol) in CH_2Cl_2 (20 mL) at -78°C under argon followed by dropwise additon of $SnCl_4$ (0.47 mL, 4.0 mmol). The dark red solution was stirred for 5 min, diluted with diethyl ether and washed with saturated $NaHCO_3$ and brine, dried and concentrated. The crude hydroxy ester **11** was then hydrolysed by refluxing for 5 h in a mixture of THF (10 mL), MeOH (20 mL) and 1M aqueous NaOH (10 mL). After cooling to room temperature the reaction mixture was extracted with heptane. The organic layer was washed with 1M NaOH, dried and concentrated to give crude (-)-8-phenylmenthol (0.96 g) and the combined aqueous layers were acidified with 2 M HCl and extracted with diethyl ether. The organic phase was washed with brine, dried and concentrated to give the

crude hydroxy acid, which was dissolved in benzene (10 mL) containing DBU (0.73 mL, 4.95 mmol) and EtBr (0.79 mL, 10.0 mmol). The resulting mixture was heated at reflux for 5 h, cooled to room temperature, diluted with diethyl ether, washed with 2M HCl, saturated $NaHCO_3$ and brine. The organic layer was dried and concentrated and the residue was chromatographed (heptane-EtOAc, 5:1-2:1) to give (S)-(+)-**9** (0.71 g, 67 %); $[\alpha]_D^{25}$ +1° (c 0.8 $CDCl_3$). The ee was determined to be >99 % by GC and ^1H NMR analysis of the corresponding Mosher ester[24].

A solution of (S)-(+)-**9** (2.8 g, 8.7 mmol), imidazol (1.7 g, 20 mmol) and TBSCl (1.5 g, 10 mmol) in DMF (20 mL) was stirred over night. The reaction mixture was then diluted with diethyl ether, washed with 1M HCl, saturated $NaHCO_3$ and brine, dried and concentrated. Flash chromatography of the residue (heptane-EtOAc, 10:1) gave **12** (3.6 g, 95 %); $[\alpha]_D^{25}$ -23° (c 1.2, $CDCl_3$). ^1H NMR δ 7.29 (m, 2 H), 6.90 (m, 2 H), 4.43 (s, 2 H), 4.12-4.33 (m, 3 H, OCH_2CH_3, 2-H), 4.03 (s, 2 H), 3.79 (s, 3 H, OCH_3), 2.62 (m, 2 H, 3-H), 1.73, 1.77 (2 s, 6 H, CH_3), 1.29 (t, 3 H, J 10.5 Hz, OCH_2CH_3), 0.91 (s, 9 H, $SiC(CH_3)_3$), -0.02, 0.04 (2 s, 6 H, $Si(CH_3)_2$). Anal. Calcd for $C_{20}H_{34}O_2$: C, 66.08; H, 9.19. Found: C, 65.91; H, 9.37.

Ethyl (4S)-(2Z)-4-[(t-butyldimethylsilyl)oxy]-3-[(diethylphosphoryl)oxy]-6-[(4-methoxybenzyloxy)methyl]-7-methyl-2, 6-octadienoate, (13). n-BuLi (33.3 mL, 70.0 mmol, 2.1 M in hexane) was added to a solution of hexamethyldisilazane (16.0 mL, 76.8 mmol) in THF (55 mL) at 0°C under argon. The reaction mixture was cooled to -70°C and EtOAc (3.43 mL, 35.0 mmol) was added slowly. The solution was stirred for 10 min and a solution of compound **12** (10.2 g, 23.4 mmol) and TMEDA (10.4 mL, 70.0 mmol) in THF (15 mL) was added. The cooling bath was removed and the mixture was stirred for 30 min The mixture was diluted with diethyl ether, washed with 1M HCl and brine, dried and concentrated. The crude β-keto ester was dissolved in THF (60 mL) and t-BuOK (2.72 g, 24.3 mmol) was added. After stirring for 3 min, diethylchlorophosphate (4.2 mL, 34.0 mmol) was added and the reaction mixture was stirred for 15 min Diethyl ether was added and the reaction mixture was washed with 10 % NH_4Cl and water, dried and concentrated. Chromatography of the residue (heptane-EtOAc, 5:1-1:1) gave **13** (9.0 g, 62 %); $[\alpha]_D^{25}$ +2°(c 1.0, $CDCl_3$).^1H NMR δ 7.26 (d, 2 H, J 8.8 Hz), 6.87 (d, 2 H, J 8.8 Hz), 5.81 (m, 1H, 2-H), 4.51-4.58 (m, 1 H, 4-H), 4.39 (2 d, 2 H, J 11.5 Hz), 4.10-4.30 (m, 6 H, OCH_2CH_3), 4.01 (s, 2 H), 3.80 (s, 3 H, OCH_3), 2.68 (dd, 2 H, J 2.4, 13.7 Hz, 5-H), 2.42 (dd, 1 H, J 9.2, 13.7 Hz, 5-H), 1.71, 1.76 (s, 6 H, CH_3), 1.25-1.37 (m, 9 H,

OCH_2CH_3), 0.88 (s, 9 H, $SiC(CH_3)_3$), -0.06, 0.04 (2 s, 6 H, $Si(CH_3)_2$). CIMS m/e 615 (M+1). HRMS calcd for $C_{22}H_{42}O_7SiP$: 477.2437. Found: 477.2436 (M-methoxybenzyloxy).

Ethyl (4S)-(2Z)-4-[(t-butyldimethylsilyl)oxy]-6-hydroxymethyl-7-methyl-3-[(trimethylsilyl)methyl]-2, 6-octadienoate, (14). $TMSCH_2MgCl$ (13.0 mL, 13.0 mmol, 1M in diethyl ether) was added to a solution of compound **13** (4.0 g, 6.5 mmol) in diethyl ether at 0°C under argon. $Ni(acac)_2$ (0.13 g, 0.5 mmol) was added in portions during 30 min[21] The mixture was diluted with diethyl ether, washed with 2M HCl, saturated $NaHCO_3$ and brine, dried and concentrated. Flash chromatography of the residue (heptane-EtOAc, 20:1-3:1) gave ethyl (4S)-(2Z)-4-[(t-butyldimethylsilyl)oxy]-6-[(4-methoxybenzyloxy)methyl]-7-methyl-3-[(trimethylsilyl)methyl]-2, 6-octadienoate (2.3 g, 65 %). $[\alpha]_D^{25}$ +53° (c 0.7, $CDCl_3$).

DDQ (1.24 g, 5.47 mmol) was added in portions to a solution of this PMB protected allylic silane (2.3 g, 4.2 mmol) in CH_2Cl_2 (40 mL) and water (2 mL) at 0°C.[23] The reaction mixture was stirred for 60 min and then $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2, the combined organic extracts were washed with $NaHCO_3$ and brine, dried and concentrated. Since the crude product contained some overoxidized material (aldehyde) it was dissolved in MeOH (10 mL) and $CeCl_3 \cdot 7\ H_2O$ (0.78 g, 2.1 mmol) was added followed by $NaBH_4$ (80 mg, 2.1 mmol). The reaction mixture was stirred for 10 min and then 1M HCl was added and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried and concentrated. Chromatography of the residue (heptane-EtOAc, 30:1-10:1), gave **14** (1.5 g, 85 %) having identical ^1H NMR spectral data as previously described[7]; $[\alpha]_D^{25}$ +68° (c 0.7, $CDCl_3$) (Lit.[7] $[\alpha]_D^{20}$ +70° (c 0.60, $CDCl_3$)).

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14. Our previous choice of protecting groups as in **4** was unexpectedly problematic since at a later stage the THP protection could not be selectively removed in the presence of the t-butyldimethylsilyl (TBS) ether grouping. After some experimentation we arrived at the use of pyridinium tosylate in *iso*-propanol as the best, but still not highly selective, conditions for the removal of the THP ether. The use of p-methoxybenzyl (PMB) protection instead of the THP protection avoids this problem.
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