A Synthesis of Taxanes by Lactam-sulfoxide Ring Contraction and Intramolecular Pinacol Coupling

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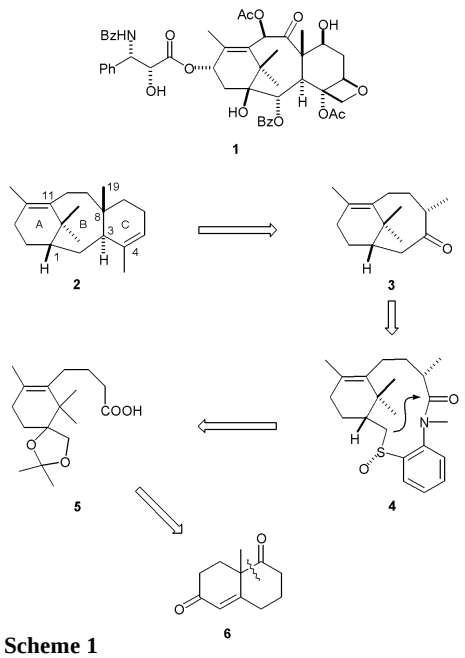
Abstract: A synthesis of the taxane ring system is described. The A-ring moiety **5**, containing the carbons for construction of the B-ring, was prepared from Wieland-Miescher ketone via Beckmann fragmentation of the oxime **10**. The B-ring was formed by means of 12-membered lactam-sulfoxide ring contraction. The formation of the C-ring was carried out by aldol condensation of the resulting AB-ring moiety **3** followed by intramolecular pinacol coupling to give the tricyclic diol **23**.

Key words: taxane, ring contraction, SmI_2, pinacol coupling, Beckmann fragmentation

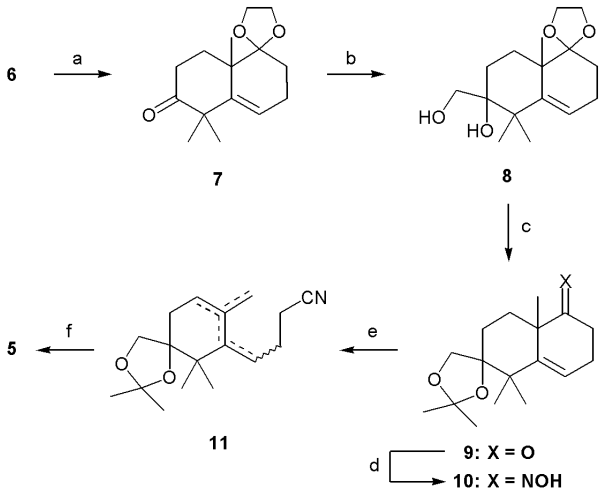
Taxol® (paclitaxel, **1**), isolated from *Taxus brevifolia*,[1] is a clinically useful antimitotic agent and its total synthesis has already been achieved.[2] The taxane framework is a tricyclic ring system containing a highly strained 8-membered ring as the B ring, and many approaches to this ring system have been developed.[3] In the biosynthesis of **1**, the initial step is cyclization of geranylgeranyl diphosphate to taxa-4(5),11(12)-diene (**2**).[4] But the nature of the subsequent oxidation process from **2** to **1** has not been reported.[4b] In preparation for tracer experiments with ^{13}C-labeled derivatives, we examined the synthesis of **2** and its oxidation products.[5]



Scheme 1

Our synthetic plan is shown in Scheme 1. The B-ring of ketone **3**, a key intermediate in the synthesis, is constructed by means of the lactam-sulfoxide ring contraction.[6] The lactam-sulfoxide **4** containing the *o*-thioaniline moiety as a spacer is formed from carboxylic acid **5**, which is prepared from the Wieland-Miescher ketone (**6**) by cleavage of the bond between the quaternary carbon and the carbonyl carbon.

Ketone **7** was selected as starting material and prepared from **6** in 2 steps by known methods (Scheme 2).[7] Wittig reaction of **7** and selective oxidation of the resulting *exo*-olefin with OsO_4 in the presence of NMO gave the diol **8** as a 3:2 diastereomeric mixture. Acetonide formation and hydrolysis of the ketal in **8** proceeded in one pot under acidic conditions in acetone to give ketone **9**. Cleavage of the bond between the quaternary carbon and the carbonyl carbon in **9** was achieved by Beckmann fragmentation[8] of the oxime **10** with TsCl in pyridine to afford a mixture of the dienes **11**. Hydrolysis of the cyano group of **11** with KOH, followed by Birch reduction gave carboxylic acid **5**, which contains all the carbons of the AB-ring moiety and the desired tetrasubstituted olefin in the A-ring.[9]



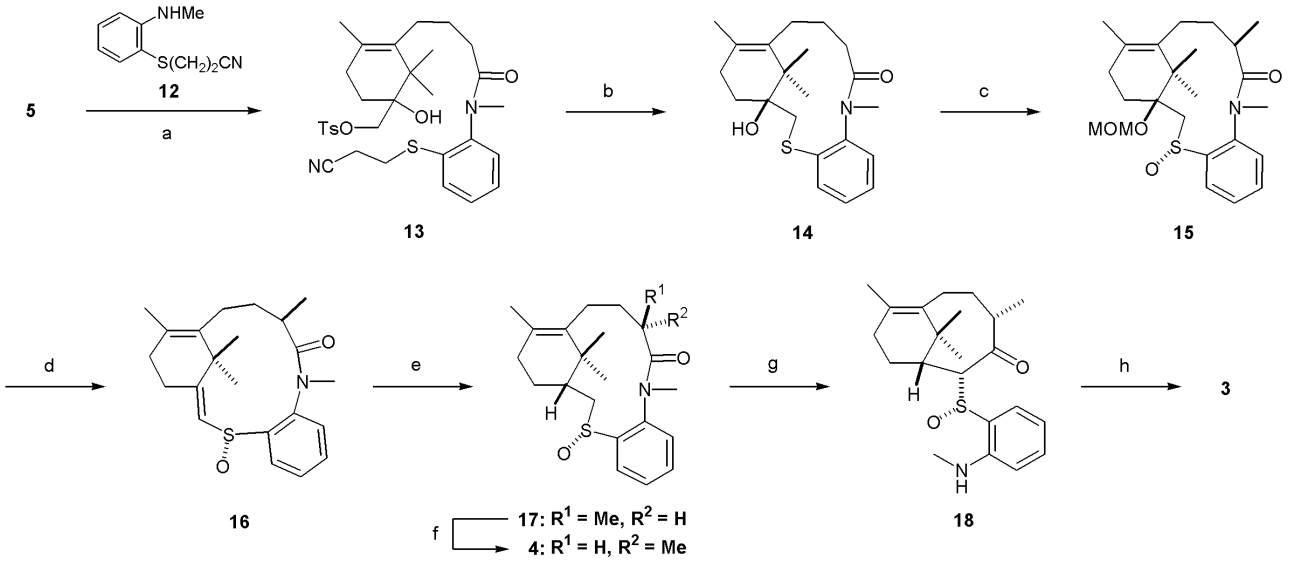
Reagents and conditions: a) see ref. 7; b) NaH, Ph_3PCH_3Br, DMSO, 60 °C; OsO_4, NMO, acetone-H_2O, r.t.; c) *p*-TsOH, acetone, reflux, 96% from **7**; d) NH_2OH•HCl, Py, r.t., 98%; e) *p*-TsCl, Py, reflux, 71%; f) KOH, EtOH, reflux; Li, NH_3, THF, -78 °C, 72% from **11**.

Scheme 2

Construction of the strained B-ring was achieved stepwise by cyclization of **5** to a 12-membered ring lactam-sulfoxide including the spacer moiety and ring contraction to an 8-membered ring (Scheme 3). Condensation of **5** and the *o*-thioaniline **12**, prepared by hydrolysis of 3-methylbenzothiazole-2-thione with KOH and conjugate addition of the resulting thiol to acrylonitrile,[6b] *via* the acid chloride of **5**, followed by hydrolysis of the acetonide and tosylation of the resulting primary alcohol, gave the amide **13**. Cyclization of **13** was accomplished by slow dropwise addition of **13** to a mixture of K_2CO_3 and $NaBH_4$ in *N*,*N*-dimethylacetamide (DMA) and ethylene glycol at 130 °C under high dilution conditions[6] to afford the 12-membered lactam-sulfide **14**. In this reaction, the 2-cyanoethyl *S*-protective group was eliminated, and the resulting thiol-tosylate was cyclized to **14**. The presence of $NaBH_4$ prevented the formation of disulfide from the thiol, and the produced acrylonitrile was reduced to propionitrile to avoid the reverse reaction to **13**. After protection of the tertiary hydroxyl group in **14** with a MOM group, introduction of the methyl group corresponding to C19[10] at the α-position of the amide carbonyl with LDA and MeI proceeded with high diastereoselectivity, and oxidation of the sulfur with $NaIO_4$ afforded the sulfoxide **15** as a single isomer. Treatment of **15** with LDA caused β-elimination of the MOMO group and afforded the vinylsulfoxide **16**. The chemical structure of **16** was confirmed by X-ray crystallographic analysis.[11] Selective reduction of the olefin adjacent to sulfur in **16** with $LiBHEt_3$ proceeded through peripheral attack of hydride at C1 to give the lactam-sulfoxide **17**. Since ring contraction of **17** did not proceed, ring contraction of **4**, a diastereomer of **17** with respect to the methyl group at the α-position of the amide carbonyl, was examined. Isomerization of **17** with *t*-BuOK gave **4** with complete stereoselectivity. The stereochemistry of **4** was determined by X-ray crystallographic analysis.[12] Ring contraction of **4** was achieved by treatment with LDA to give the desired 8-membered ketone **18**. The synthesis of the AB-ring moiety **3** was finished by reductive removal of the spacer moiety of **18** with Na-Hg.[13] The stereochemistry of **3** was determined from difference NOE spectra.

Construction of the C-ring was performed by the introduction of a four-carbon side chain corresponding to C4-7 into the AB-ring moiety **3** at C8 and cyclization between C3 and C4, by means of aldol condensation and SmI_2-induced intramolecular pinacol coupling (Scheme 4). Aldol condensation of **3** at C8, the more substituted α-carbon, with LDA and aldehyde **19** afforded a 2:1 mixture of β-hydroxyketones in excellent yield. The mixture of β-hydroxyketones was converted without separation to the MOM ethers **20** and **21**. The relative stereochemistry of C19 and the proton adjacent to C1 in **20** and **21** was *syn*, as determined by difference NOE experiments, and the *anti* isomers were not observed. Removal of the TBS group of the major isomer **20** with TBAF and Dess-Martin oxidation[14] of the resulting primary alcohol gave aldehyde **22**. Cyclization of the C-ring was achieved by treatment of **22** with SmI_2 in THF[15] under reflux conditions to afford the tricyclic diol **23**.[16] The stereochemistry of the two hydroxyl groups of **23** was *syn* and the BC ring junction was *trans*, as in natural taxanes, as judged from an X-ray crystallographic analysis.[17]

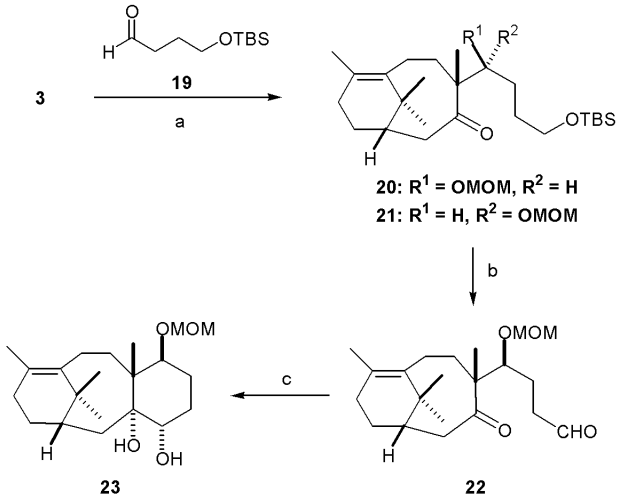
Thus, the synthesis of the tricyclic ring system of taxanes was accomplished by means of lactam-sulfoxide ring contraction to form the B-ring and SmI_2-induced intramolecular pinacol coupling to form the C-ring. The result-



Reagents and conditions: a) $(COCl)_2$, benzene, then **12**, r.t.; 1N HCl, MeOH, r.t.; *p*-TsCl, Py, r.t., 77% from **5**; b) K_2CO_3, $NaBH_4$, $(CH_2OH)_2$, DMA, 130 °C, 95%; c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, r.t., quant.; LDA, MeI, THF, -78 °C, 99%; $NaIO_4$, MeOH, H_2O, r.t., quant.; d) LDA, THF, -78°C, 95%; e) $LiBEt_3H$, THF, r.t., 84%; f) *t*-BuOK, DMSO, THF, r.t., 91%; g) LDA, THF, -78°C then r.t.; h) 5% Na-Hg, Na_2HPO_4, MeOH, Et_2O, r.t., 80% from **4**.

Scheme 3

ing tricyclic diol **23** may be further manipulated to extend the synthesis to taxadienes, and should be useful for studies on Taxol® (**1**) biosynthesis.



Reagents and conditions: a) LDA, THF, -20 °C, then **19**, -78 °C; MOMCl, *i*-Pr_2NEt, CH_2Cl_2, r.t., 89% from **3**; b) TBAF, THF, r.t.; Dess-Martin reagent, Py, CH_2Cl_2, r.t., 91% from **20**; c) SmI_2, THF, reflux, 43%.

Scheme 4

Acknowledgement

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References and Notes

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(9) **5**: mp. 69.1–71.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.99 (3H, s), 1.09 (3H, s), 1.40 (3H, s), 1.44 (3H, s), 1.63 (3H, s), 1.65–1.77 (3H, m), 1.85–2.08 (4H, m), 2.21 (1H, m), 2.38 (2H, t, *J* = 7.2 Hz), 3.67 (1H, d, *J* = 8.8 Hz), 3.94 (1H, d, *J* = 8.8 Hz); IR (neat) cm^{-1}: 3590–2350 (br), 1709, 1457, 1381, 1371, 1261, 1216, 1159, 1046, 870; EI-MS *m/z* (%): 296 (M^+, 6), 221 (12), 182 (100), 167 (20), 122 (18), 107 (17).
(10) The taxane numbering system is used throughout.
(11) Crystal system of **16**: orthorhombic; unit-cell dimensions: *a* = 14.877 (3) Å, *b* = 43.434 (7) Å, *c* = 11.897 (2) Å; volume of unit cell: 7688 (2) Å^3; *Z* value: 16; space group: *Fdd2*; residuals: *R* = 2.4%, *wR* = 3.7%.
(12) Crystal system of **4**: orthorhombic; unit-cell dimensions: *a* = 10.028 (2) Å, *b* = 21.865 (5) Å, *c* = 9.294 (2) Å; volume of unit cell: 2038.0 (6) Å^3; *Z* value: 4; space group: $P2_1cn$; residuals: *R* = 3.0%, *wR* = 4.8%.
(13) A synthesis of a diastereomeric mixture of **3** has been reported, see: Martin S. F.; Assercq, J.-M.; Austin R. E.; Dantanarayana, A. P.; Fishpaugh, J. R.; Gluchowski, C.; Guinn, D. E.; Hartmann, M.; Tanaka, T.; Wagner, R.: White, J. B. *Tetrahedron* **1995**, *51*, 3455. **3**: mp. 29.0–31.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (3H, d, *J* = 6.6 Hz), 1.05 (3H, s), 1.43 (3H, s), 1.44 (3H, s), 1.59 (1H, m), 1.70–2.15 (7H, m), 2.22 (1H, ddd, *J* = 5.0, 11.5, 14.0 Hz), 2.34 (1H, m), 2.83 (1H, m), 2.90 (1H, dd, *J* = 5.5, 11.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.7, 20.3, 24.0, 25.1, 27.4, 28.2, 29.8, 37.0, 37.8, 46.1, 49.7, 50.6, 134.2, 136.6, 218.6; IR (neat) cm^{-1}: 2938, 1688, 1458, 1370, 1202, 1184, 1113, 1066, 1037; HR-MS *m/z* : Calcd for $C_{15}H_{24}O$: 220.1827. Found: 220.1825 (M^+); EI-MS *m/z* (%): 220 (M^+, 27), 205 (20), 202 (60), 187 (39), 163 (27), 150 (100), 147 (37), 145 (24), 121 (38), 119 (22), 109 (24), 107 (29), 105 (21).
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(16) **23**: mp. 146.5–147.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.03 (3H, s), 1.04 (3H, s), 1.32 (3H, s), 1.46 (2H, m), 1.72-2.13 (10H, m), 1.81 (3H, s), 2.19 (1H, d, *J* = 8.6 Hz), 2.28 (1H, ddd, *J* = 3.4, 15.3, 16.8 Hz), 2.41 (1H, dd, *J* = 6.0, 16.8 Hz), 2.43 (2H, m), 3.09 (1H, m), 3.26 (1H, dd, *J* = 4.3, 11.6 Hz), 3.36 (3H, s), 4.57 (1H, d, *J* = 6.7 Hz), 4.65 (1H, d, *J* = 6.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 147.7, 126.8, 96.9, 83.1, 80.4, 73.4, 55.8, 48.7, 47.9, 38.4, 35.7, 34.5, 29.3, 29.1, 28.3, 27.0, 26.0, 23.0, 22.9, 21.6, 13.9; IR (neat) cm^{-1}: 3505, 3463, 2951, 2880, 1100, 1034, 911; HR-MS *m/z*: Calcd for $C_{21}H_{36}O_4$: 352.2613. Found: 352.2619 (M^+); EI-MS *m/z* (%): 352 (M^+, 26), 219 (22), 203 (60), 201 (27),187 (24), 173 (27), 171 (22), 159 (46), 145 (49), 143 (24), 136 (24), 135 (63), 134 (34), 133 (67), 131 (39), 123 (42), 122 (32), 121 (100), 120 (31), 119 (93), 117 (26), 111 (29), 109 (63), 107 (94), 105 (93); *Anal*. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.30; H, 10.07.
(17) Crystal system of **23**: monoclinic; unit-cell dimensions: *a* = 12.979 (2) Å, *b* = 19.573 (3) Å, *c* = 7.770 (2) Å, β = 101.35 (1) degree; volume of unit cell: 1935.3 (6) Å^3; *Z* value: 4; space group: $P2_1/n$; residuals: *R* = 3.4%, *wR* = 3.4%.

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