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Studies Towards the Total Synthesis of Taxoids. Lead Tetraacetate Oxidations of Selected Unsaturated Bicyclic Diols

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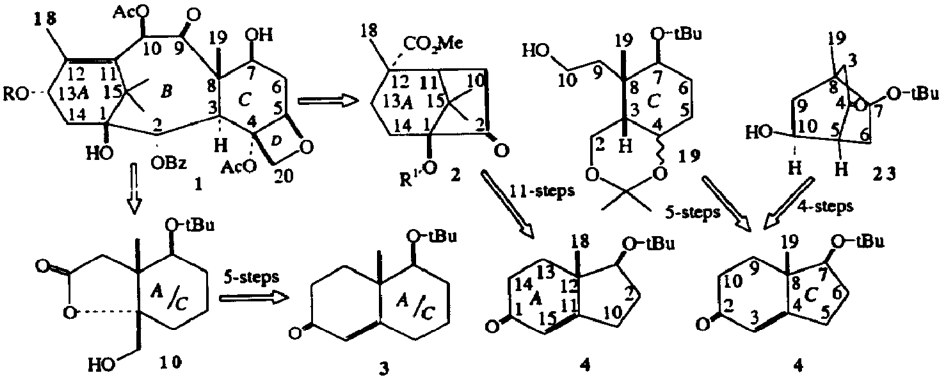
Abstract: *Syntheses of potential C-1/C-15 and C-2/C-10 subunits of taxoid skeleton* ***1*** *using lead tetraacetate cleavage of the Wieland-Miescher ketone derived diol* ***6*** *and the Hajos-Parrish ketone derived diol* ***14*** *are described.*

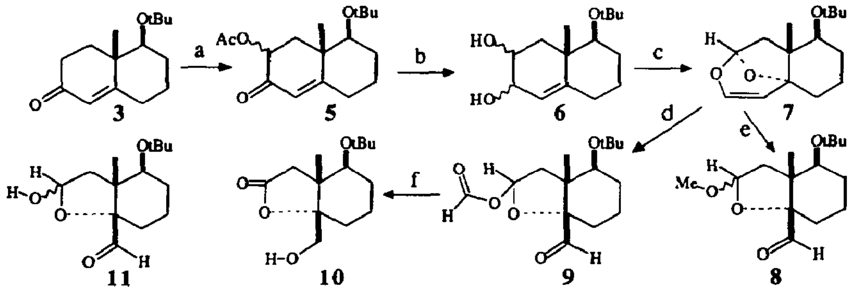
We have reported[1] the use of (S)-(+)-Hajos-Parrish ketone to synthesize the bicyclo[3.2.1]octane derivative **2**, a homochiral taxol A ring precursor. Continuing our efforts towards the total synthesis of taxoids, using the (S)-(+)-Wieland-Miescher and (S)-(+)-Hajos-Parrish ketones as building blocks for either the A or C rings, we investigated the oxidative cleavage of unsaturated diols **6** and **14**. The lead tetraacetate treatment [2] of these diols followed an unsuspected course, and thus provided a convenient route to multigram quantities of **10**, **11**, **20** and **23**, possessing functionality and absolute configuration that are appropriate for elaboration of the A and C ring components of taxoids (Scheme 1). Cleavage of unsaturated α-ketols has been reported recently by Watt et al.,[3] in their synthetic project of taxoids where both the A and C rings derive from the (S)-(+)-enantiomer of Wieland-Miescher ketone.



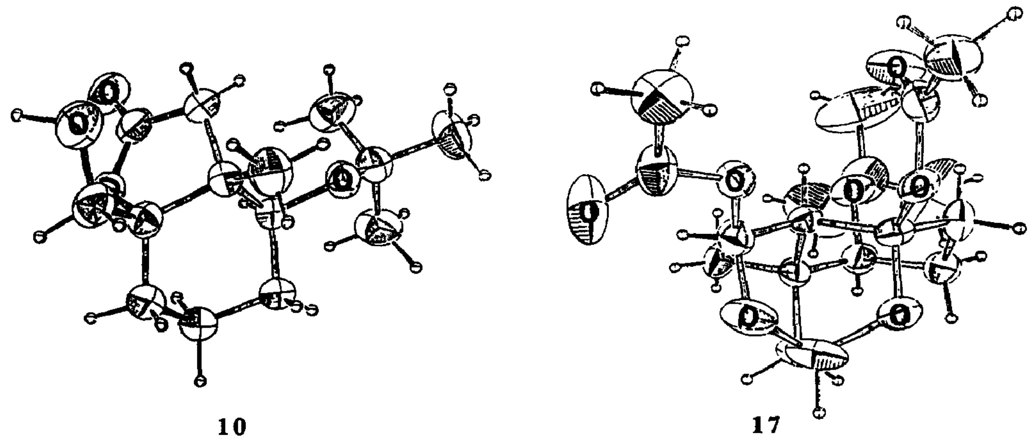
Scheme 1

The diastereomeric mixture **5**,[4] obtained in 94% yield from the 9-OtBu protected Wieland-Miescher ketone derivative **3**, upon treatment with lead tetraacetate (4 equiv., refluxing benzene, 4 days, N_2),was reduced to the diastereomeric mixture of diols **6** (L-Selectride, THF, -70°C to r.t., 1h, then 15% NaOH and

30% H_2O_2). Treatment of the latter with lead tetraacetate (2 equiv., in acetonitrile, -25°C to r.t., 3h) afforded 7[5] in 91% yield after silica gel flash chromatography, (heptane-ether 1:1). Ozonolysis of 7 in methanol (-78°C, then PPh_3) afforded a diastereomeric mixture of 8 in 62% yield and 6:1 ratio. When the ozonolysis was performed in dichloromethane, aldehyde 9 was obtained which, upon base treatment (K_2CO_3, MeOH-H_2O, 10h), afforded **10** (m.p. 104-5°C, ether) in 50% yield, presumably via a Cannizzaro type reaction.[6] The structure of the bicyclic lactone **10** thus obtained was assigned by comprehensive spectral data (400MHz ^{1}H-NMR, 1 and 2D experiments) and was confirmed by a single-crystal X-ray analysis (Figure 1). When the base treatment was stopped after only 5 min, a diastereomeric mixture of lactols **11** was obtained.



Scheme 2: a) $Pb(OAc)_4$/PhH b) L-Selectride/THF, -70°C, then NaOH-H_2O_2 c) $Pb(OAc)_4$/CH_3CN d) O_3/CH_2Cl_2, -78°C e) O_3/MeOH, -78°C f) K_2CO_3-MeOH-H_2O.

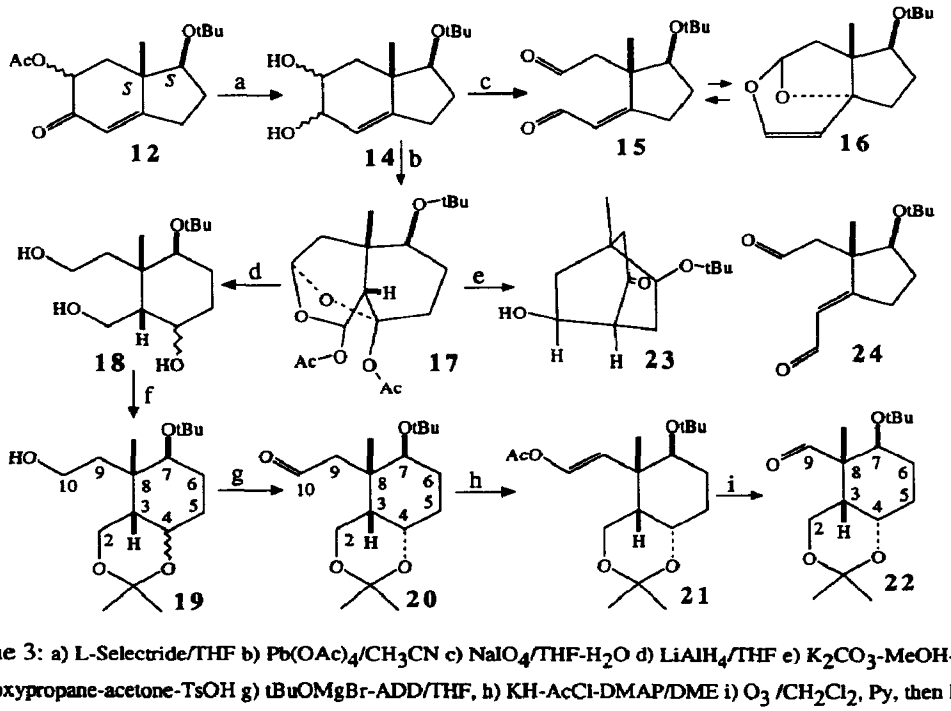


10 17

Figure 1: Computer generated drawings of **10** and **17** derived from X-ray coordinates

The procedure used to prepare the C-ring precursors[7] **19, 22, 23** is outlined in Scheme 3. Enantiomerically pure (S)-(+)- and (R)-(-)-Hajos-Parrish ketones were converted by known protocols[8] to the acetoxyenone derivatives **12** and **13** respectively which were then reduced (L-Selectride, THF, -70°C to r.t., 1h, then 15% NaOH, 30% H_2O_2) to the unsaturated diols **14** and ent-**14** (96%) prior to oxidation. Thus, treatment of **14** with 3 equiv. of $Pb(OAc)_4$ in acetonitrile (-25°C, then r.t. , 16h) followed by filtration through Celite and silica gel afforded **17** (m.p. 103-4°C, pentane-ether) in 80% isolated yield.

When the reaction was stopped after only 5 min., a mixture of **15** and **16** in 1:1 ratio (^{1}H-NMR) was obtained in 86% yield. The E-dialdehyde **24** obtained from **14** via a sodium periodate cleavage (3.5 equiv., THF-H_2O, r.t., 2h, 86%) remained unchanged upon treatment with lead tetraacetate as above. The structure of **17**, was unambiguously established by X-ray analysis (Figure 1). Conversion of **17** to **19** was accomplished by reduction with excess $LiAlH_4$ to the triol **18** (9:1 epimeric mixture, 70% yield) and subsequent selective acetonide formation (2,2-dimethoxypropane, acetone, TsOH, r.t., 5 min) in quantitative yield. Oxidation with 1,1'-(azodicarbonyl)dipiperidine (tBuOMgBr, THF, 0°C, then ADD, THF, 0°C to r.t., 1h)[9] of the major (syn) acetonide **19** (m.p.72-3°C, pentane-ether) led in 89% yield to the corresponding aldehyde **20** (m.p. 52-3°C, pentane), a useful taxoid C-ring building block, containing 10 out of the 20 carbon atoms, oxygen functionalities at C-2, C-4, C-7, C-10 and the required absolute configuration on C-8, C-7. Searching for a C-ring component suitable for a C-9/C-10 coupling, we further transformed **20** to **22** (m.p. 63-4°C, pentane) through its enol acetate[10] **21** (KH, DME, -5°C, 15 min for the enolate formation, then AcCl, DME, DMAP, r.t., 15 min) and subsequent ozonolysis (O_3, CH_2Cl_2, Py, -70°C, then PPh_3) in 61% yield from **20**. Elaboration of **12** into **23** requires only 4 steps and proceeds in 71% overall yield. Base treatment of **17** (K_2CO_3, MeOH-H_2O, r.t., 15h) led to **23** (m.p. 94-5°C, pentane) in 92% yield.



Scheme 3: a) L-Selectride/THF b) $Pb(OAc)_4/CH_3CN$ c) $NaIO_4$/THF-H_2O d) $LiAlH_4$/THF e) K_2CO_3-MeOH-H_2O f) 2,2-dimethoxypropane-acetone-TsOH g) tBuOMgBr-ADD/THF, h) KH-AcCl-DMAP/DME i) O_3 /CH_2Cl_2, Py, then PPh_3.

In the case of the decalone derivative **6**, we believe the reaction to proceed through the formation of a dialdehyde followed by an intramolecular Michael addition resulting in the construction of the tricyclic product **7**. We favour an alternative mechanism for the hydrindenone derivative **14** consisting of an initial intramolecular 1,4-addition to the enal **15**, leading to the tricyclic compound **16** followed by diacetylation of the enol ether part [11] and subsequent ring enlargement involving the derived diacetate leading to **17**. It appears that ring strain provides a sufficient driving force to effect this rearrangement. Regardless of which mechanism is operative, **7** and **17** are useful synthetic intermediates for the "A" and "C" rings of taxoids.

In summary, we describe here a straightforward and versatile method for the preparation of appropriately substituted homochiral cyclohexanes from simple precursors. Studies to evaluate the scope and effectiveness of these transformations as well as to get some mechanistic insight are under way.[12]

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4. Racemic **5** was subjected to enzymatic hydrolysis by employing horse liver esterase to yield the (R)-acetate and the (S)-alcohol thus exhibiting an (S)-specificity. To be published elswhere.
5. **mp** 39-40°C (pentane); **IR** (film) ν 2969, 2938, 2869, 1725, 1638, 1456, 1362, 1281, 1206, 1131, 1069, 1019, 994, 938 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 1.07 (3 H, s), 1.18 (9 H, s), 1.31 (1 H, m), 1.35 (1 H, m), 1.55 (1 H, m.); 1.61 (1 H, m), 1.70 (1 H, ddt, J = 1.7, 3.3, 12.9 Hz), 1.86 (1 H, dd, J = 1.2, 14.3), 1.91 (1 H, d quintet, J = 1.7, 14.5 Hz), 2.44 (1 H, dd, J = 5.8, 14.3 Hz), 3.37 (1 H, dd, J = 3.6, 11.4 Hz), 4.75 (1 H, d, J = 6.1 Hz), 5.63 (1 H, d, J = 5.8 Hz), 6.18 (1 H, d, J = 6.1 Hz); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 12.5, 19.8, 28.9, 29.3, 29.7, 46.7, 55.4, 73.5, 84.5 , 99.4, 110.0, 135.5; **EIMS:** m/z 252 ($M^{+\cdot}$ 26), 196 (50), 195 (30), 57 (100).
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