From Toluene to Taxol™: Chemoenzymatic and Enantiodivergent Routes to the AB-Ring Systems of Taxoids and *ent*-Taxoids

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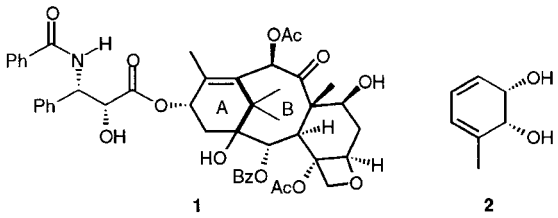
Received 22 April 1998

Abstract: The *cis*-1,2-dihydrocatechol **2** has been converted, *via* reaction sequences including Diels-Alder cycloaddition and anionic oxy-Cope rearrangement steps, into the enantiopure bicyclo[5.3.1]undecanes **20** and **33** which correspond to the AB-ring systems of *ent*-taxoids and taxoids, respectively.

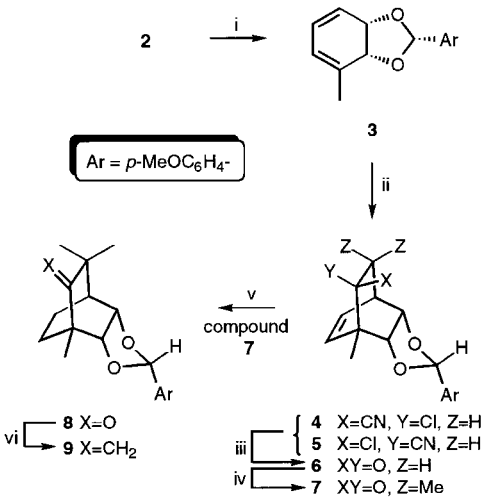
The taxoid diterpenes have attracted enormous attention from synthesis chemists because of their challenging molecular architectures and because certain members of this class of compound, most notably Taxol™ (paclitaxel, **1**), display clinically useful anti-tumour properties.[1] Many elegant approaches to and some seven total syntheses of taxoid natural products have been developed in recent years.[2] Martin and co-workers have demonstrated,[3] using racemic materials, that anionic oxy-Cope rearrangement[4] of 2-alkenyl-6-methylenebicyclo[2.2.2]octan-2-ols provides an especially attractive means for preparing the bicyclo[5.3.1]undecanyl- or AB-ring system associated with taxoids. However, this approach is limited by the paucity of monochiral bicyclo[2.2.2]octanyl systems[5] which would allow for the synthesis of enantiopure bicyclo[5.3.1]undecenes. Since monochiral *cis*-1,2-dihydrocatechols[6] such as **2** engage, as the 4π-component, in diastereofacially selective Diels-Alder cycloaddition reactions with the resultant formation of bicyclo[2.2.2]octenes[6-8] we have investigated the possibility of elaborating these adducts into bicyclo[5.3.1]undecanones *via* anionic oxy-Cope rearrangement chemistry. We now report that by this means the *cis*-1,2-dihydrocatechol **2** (available in quantity *via* microbial oxidation of toluene) can be readily elaborated to the AB-ring system associated with EITHER taxoids OR *ent*-taxoids.



1 **2**

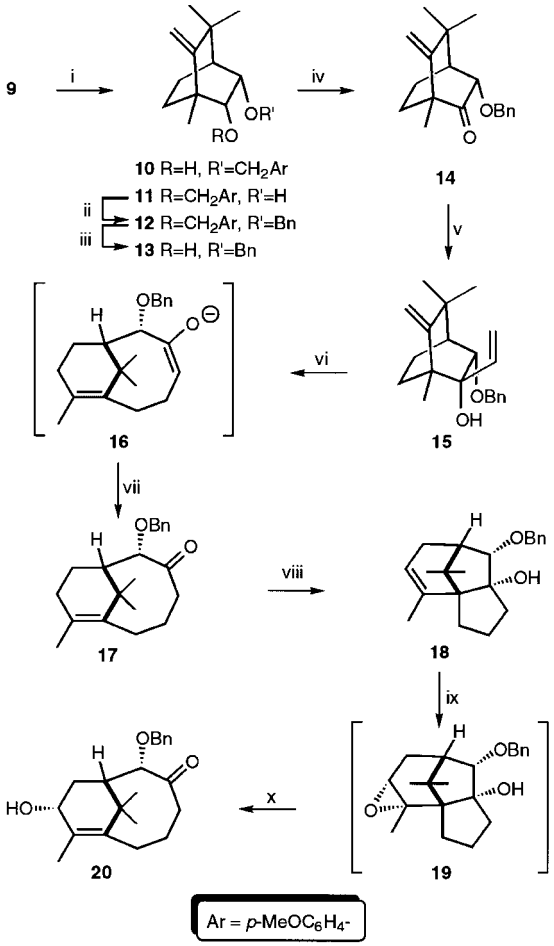
Reaction (Scheme 1) of diol **2** with *p*-methoxybenzaldehyde dimethyl acetal (*p*-MBDMA) in the presence of an acid catalyst afforded the *endo*-*p*-methoxybenzylidine acetal **3**[9] (m.p. = 101-102 °C) in 53% yield. The latter compound was subjected to thermally-promoted Diels-Alder reaction with α-chloroacrylonitrile and in this manner a 4:1 mixture of adducts **4** and **5** was obtained in quantitative yield.

Hydrolysis of chloronitriles **4** and **5** was best effected with KOH in *t*-BuOH[10] and each gave the same ketone, *viz*. compound **6** (86%) (m.p. = 136-137 °C), which could be *gem*-dimethylated using methyl iodide and sodium hexamethyldisilazide (NaHMDS). The resulting ketone **7** (89%, m.p. = 117-118 °C) was subjected to chemoselective reduction using Adams' catalyst[11] and the saturated analogue **8** (m.p. = 128.5-129 °C) obtained in quantitative yield. Further elaboration of ketone **8** necessitated olefination of the highly hindered carbonyl group and efforts to achieve this conversion by conventional means were unsuccessful. However, such difficulties could be overcome by reacting compound **8** with lithium dimethyldiphenylphosphonium diylide[12] then

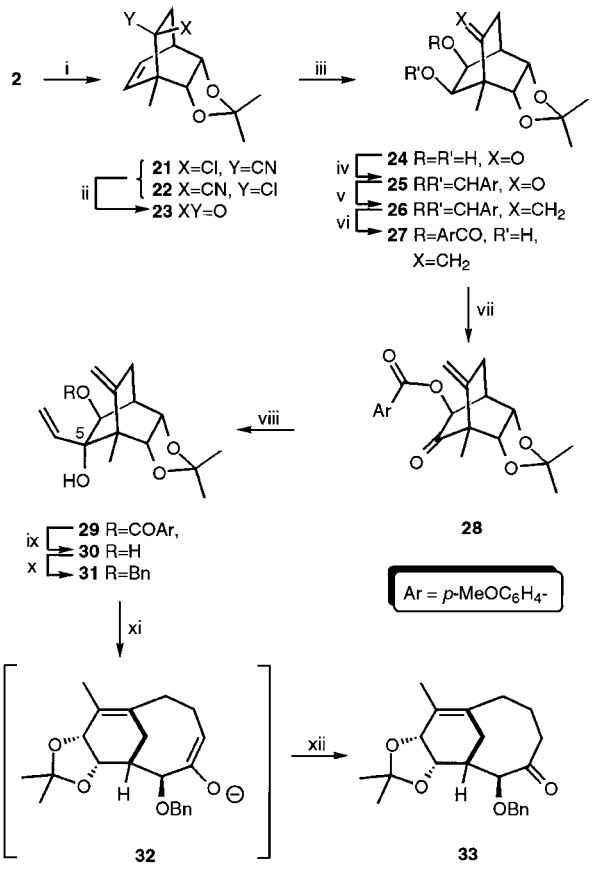


Scheme 1. *Reagents and conditions*: (i) *p*-MBDMA (1.1 mole equiv.), (+)-CSA.H_2O (0.01 mole equiv.), CH_2Cl_2, -20 °C, 0.25 h then recrystallisation (60-80 petroleum spirit); (ii) α-chloroacrylonitrile (3 mole equiv.), C_6H_6, reflux, 48 h; (iii) KOH (5 mole equiv.), ^{t}BuOH, 70° C, 1.5 h; (iv) MeI (2 mole equiv.), NaHMDS (2 mole equiv.), THF, 0 °C, 2 h then repeat x 2; (v) PtO_2 (0.2 mole equiv.), H_2, THF, 18 °C, 6.5 h; (vi) Ph_2PMe_2I (1.5 mole equiv.), *n*-BuLi (2.9 mole equiv.), THF, -10-18 °C, 2 h then **8**, 0-18 °C 1 h then ^{t}BuOH (5 mole equiv.)

quenching the reaction mixture with *t*-BuOH. By this means, alkene **9** (m.p. = 62-64 °C) was obtained in 94% yield. Reductive cleavage of the *p*-methoxybenzylidine acetal unit within compound **9** could be achieved (Scheme 2) in excellent yield (93%) using diisobutylaluminium hydride (DIBAL-H) and in this manner a 1:9 mixture of the readily separable *p*-methoxybenzyl (PMB) ethers **10** and **11** was obtained. Protection of alcohol **11** as its benzyl ether **12** (92%) was carried out under standard conditions and subsequent chemoselective cleavage of the PMB ether moiety with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded compound **13** in 97% yield. Oxidation of alcohol **13** with the Ley-Griffith reagent[13] proceeded smoothly and the resulting ketone **14** (98%) was reacted with vinylmagnesium bromide to give the 1,5-diene **15** (70%) required for the crucial anionic oxy-Cope rearrangement. Reaction of compound **15** with sodium hydride in refluxing THF resulted in a smooth rearrangement to enolate **16** which upon protonation with ammonium chloride gave bicyclo[5.3.1]undecanone **17** (90%). Compound **17** proved to be acid-sensitive and underwent a transannular ene reaction (intramolecular Prins reaction) in acidic chloroform to give tricyclic alcohol **18**.[14] On a preparative scale, this conversion was best performed using tin(II) chloride[15] and product **18** was thereby obtained in 97% yield. This reaction could be exploited for the stereocontrolled introduction of a C-13 oxygen substituent as is present in a number of important taxoids including Taxol™.[16] Thus, reaction of alkene **18** with *m*-chloroperoxybenzoic acid (*m*-CPBA) and using Na_2CO_3 as buffer afforded, *via* hydroxy-directed epoxidation, the epoxide **19**. This latter compound proved to be unstable so it was immediately converted, *via* a titanium tetraisopropoxide-promoted



Scheme 2. *Reagents and conditions*: (i) DIBAL-H (5 mole equiv., 1 M in hexane), 1:1 CH_2Cl_2/pentane, -60 °C, 4 h then -40 °C, 1.5 h; (ii) BnBr (2 mole equiv.), NaH (3.5 mole equiv.), Bu_4NI (0.1 mole equiv.), DMF, 18 °C, 15 h; (iii) DDQ (1.5 mole equiv.), 9:1 CH_2Cl_2/H_2O, 18 °C, 0.25 h; (iv) TPAP (0.05 mole equiv.), NMO (3 mole equiv.), 4 Å molecular sieves, CH_2Cl_2, 18 °C, 2.5 h; (v) $(H_2C{=}CH)MgBr$ (5 mole equiv.), THF, 0 °C, 1 h; (vi) NaH (2.5 mole equiv.), THF, reflux, 3 h; (vii) sat. aq. NH_4Cl; (viii) $SnCl_2$ (0.25 mole equiv.), $CHCl_3$, 18 °C, 1 h; (ix) *m*-CPBA (3 mole equiv.), Na_2CO_3 (8 mole equiv.), CH_2Cl_2, -15-0 °C, 7.5 h; (x) $Ti(O^iPr)_4$ (1 mole equiv.), CH_2Cl_2, reflux, 1 h. NMO = *N*-methylmorpholine *N*-oxide; TPAP = tetrapropylammonium perruthenate



Scheme 3. *Reagents and conditions*: (i) 2,2-dimethoxypropane, *p*-TsOH.H_2O (10 mole %), -10 °C, 2 h then Et_3N; α-chloroacrylonitrile (3 mole equiv.), C_6H_6, reflux 21 h; (ii) 14.3 M aq. KOH (100 mole equiv.), reflux, 16 h; (iii) OsO_4 (cat.), TMANO.$(H_2O)_2$ (2.2 mole equiv.), C_5H_5N, *t*-BuOH, H_2O, reflux, 5 h; (iv) *p*-MBDMA (1.5 mole equiv.), *p*-TsOH (cat.), THF, 0-18 °C, 16 h then Et_3N; (v) Ph_3PCH_2 (4 mole equiv.), DMSO, 65 °C, 19 h; (vi) DDQ (1.5 mole equiv.), 17:1 CH_2Cl_2/H_2O, 18 °C, 5 h; (vii) DMSO (4 mole equiv.), TFAA (3 mole equiv.), CH_2Cl_2, -60 °C, 4 h then Et_3N (excess); (viii) $(H_2C{=}CH)MgBr$ (5 mole equiv.), THF, 0-18 °C, 16 h; (ix) KOH (excess), CH_3OH, 18 °C, 16 h; (x) BnBr (1.1 mole equiv.), NaH (3.2 mole equiv.), DMF, 0-18 °C, 20 h; (xi) KH (5 mole equiv.), 18-C-6 (3 mole equiv.), THF, 0-18 °C, 1.5 h; (xii) sat. aq. NH_4Cl. TMANO = trimethylamine *N*-oxide

Eschenmoser-Grob fragmentation reaction, into the allylic alcohol **20** (82% from **18**) {$[\alpha]_D$ = +2.6° (c 1.5 in $CHCl_3$ at 20 °C}.

The reaction sequences outlined in Schemes 1 and 2 provide a means for converting *cis*-1,2-dihydrocatechol **2** into a product, **20**, which embodies the AB-ring system associated with *ent*-taxoids. Since the compound *ent*-**2** is available (in *ca*. 98% ee), *via* a two-step sequence involving microbial oxidation of *p*-iodotoluene and reductive deiodination of the resulting *cis*-1,2-dihydrocatechol,[17] then the enantiomer of compound **20** is also accessible by this same chemical pathway.

By proper positioning of the vinyl group within the bicyclo[2.2.2]octanyl framework derived from compound **2** it is also possible to produce compounds that, upon anionic oxy-Cope rearrangement, deliver bicyclo[5.3.1]undecanones corresponding to the natural series of taxoids. Such capacity for enantiodivergence is highlighted in Scheme 3. The reaction sequence starts with the 1:4 mixture of Diels-Alder adducts **21** (18%, m.p. = 178-180 °C) and **22** (70%, m.p. = 144-146 °C) obtained from the acetonide derivative of diol **2** and α-chloroacrylonitrile. Hydrolysis of this mixture gave the unsaturated ketone **23** (81%, m.p. = 81-82 °C) which was subjected to *cis*-dihydroxylation using Matteson's procedure.[18] This last reaction proceeded with high diastereoselectivity to give diol **24** (89%, m.p. = 182-182.5 °C) which was converted into the corresponding *p*-methoxybenzylidene acetal **25**[9] (79%, m.p. = 118.5-119.5 °C). Methylenation of this last compound was readily achieved using the Wittig reagent and the product of this reaction, alkene **26** (90%), was then subjected to DDQ-promoted oxidative cleavage of the acetal moiety. As a result an inseparable 1:1 mixture of diol mono-benzoate **27** and its regio-isomer was produced. This mixture was immediately subjected to Swern oxidation and the resulting ketone **28** (46% from **26**) (m.p. = 156-157 °C) and its regio-isomer (46% from **26**, m.p. = 154-156 °C) could be separated from one another by column chromatography. Reaction of compound **28** with vinylmagnesium bromide followed by hydrolysis of the resulting esters (**29** and *5-epi*-**29**) led to a *ca*. 1:3 mixture of vinylated products **30** (11%, m.p. = 72-73 °C) and *5-epi*-**30** (34%, m.p. = 138-139 °C). These two products were readily separated by column chromatography and the structure of the undesired epimer was confirmed by single crystal X-ray analysis.[19] A more selective route to the required epimer, **30**, involved hydrolysis of ester **28** to the

corresponding α-hydroxyketone (95%) (m.p. = 52-53 °C) which was then treated with vinylmagnesium bromide so as to effect a ligand assisted nucleophilic addition (LANA) reaction.[20] In this way a *ca*. 10:1 mixture **30** and *5-epi*-**30** was obtained (55% combined yield). The mono-benzyl ether **31** (53%) of diol **30** underwent smooth anionic oxy-Cope rearrangement upon treatment with KH/18-C-6 at 0-18 °C and after quenching the enolate anion **32** so-formed with saturated aqueous ammonium chloride the bicyclo[5.3.1]undecenone **33** (47%) {$[\alpha]_D$ = +38° (c 0.7 in $CHCl_3$ at 20 °C)}, which embodies the AB-ring system associated with taxoids, was obtained.

Thus, by appropriate choice of reaction pathways usefully functionalised AB-ring sub-structures (e.g. **20** and **33**) associated with both taxoids and *ent*-taxoids are accessible from the SAME readily available chiron, *viz* the toluene-derived *cis*-1,2-dihydrocatechol **2**.

Acknowledgments. We thank Drs Larry Kwart and Gregg Whited (Genencor International Inc.) for providing generous samples of compound **2**.

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