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Left-Half Taxoid Building Blocks From Hajos-Parrish Ketone

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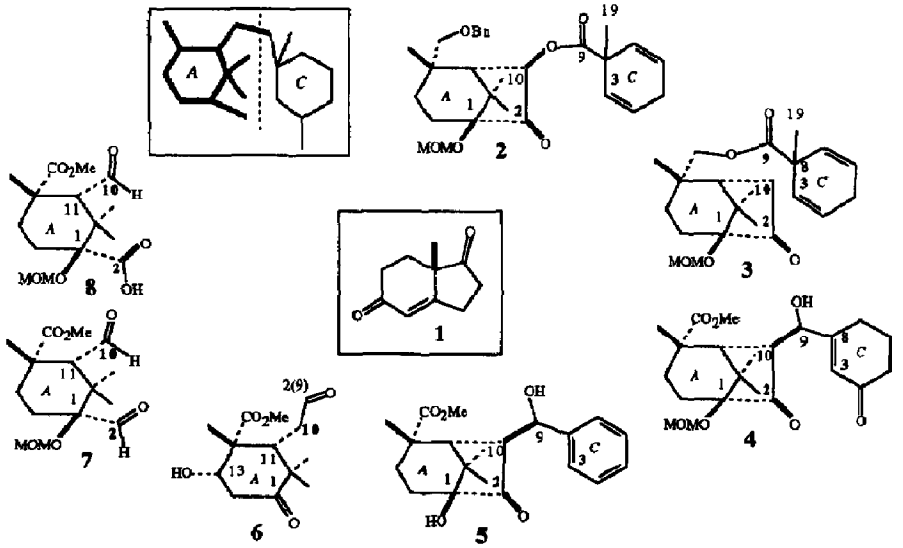
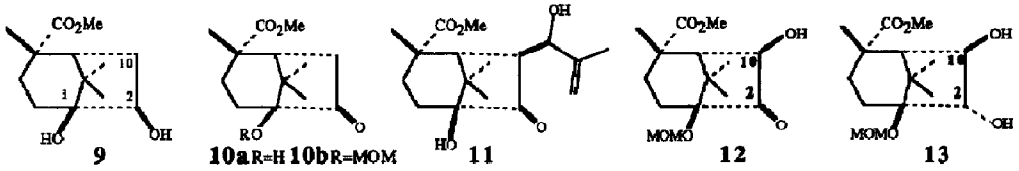
Abstract: A stereocontrolled access to the conveniently functionalized homochiral A-ring intermediates including B-seco taxanes is described.

The recent total syntheses of taxol,[1] over twenty years after its structure determination, represent the combination of dozens of man-years expended in benchwork and thinking with a touch of strategic overlapping. These syntheses are undoubtedly monumental in character nevertheless they leave much room for improvement until a viable microbial approach[2] is published. In previous reports[3] we have described methods for the preparation of both left and right-half building units from the same precursor, the (S)-(+)-Hajos-Parrish ketone **1**. We report here an efficient route to more elaborated left-half taxoid building units which either can be used in our main strategy[4] (the aldol-annelation-fragmentation , C9-C10, C2-C3, C2-/-C10, sequence) or could made use of in several other literature approaches leading to taxoid [5] and taxamycin [6] frameworks.

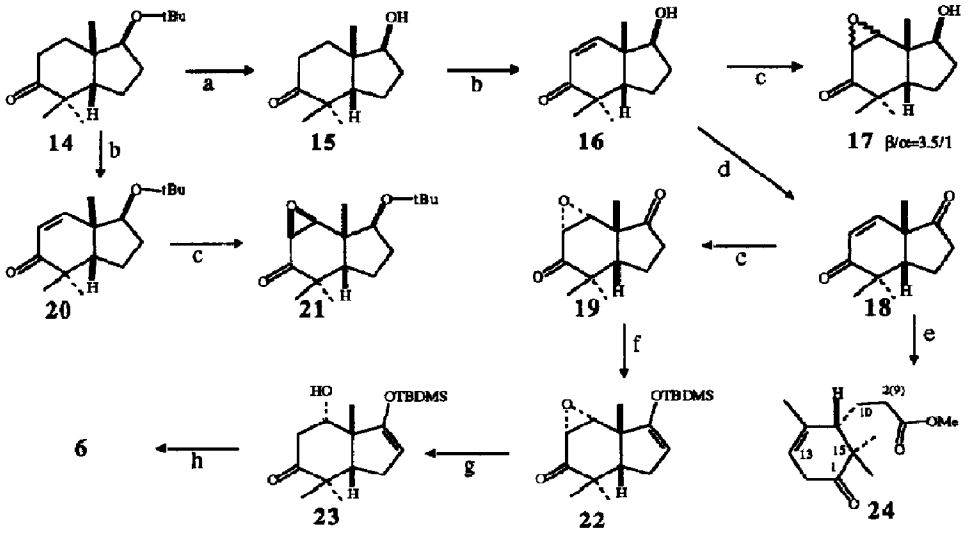


The bicyclo[3.2.1]octane derivatives **9** and **10**, obtained according to ref 3 from (S)-(+)-Hajos-Parrish ketone, served as starting materials to several A-ring substructures for an A--> AC-->ABC mode of taxoid construction. Aldol condensations (LDA, THF, -30°C, 2h, then addition of the appropriate aldehyde at -78°C,

10 min)[7] of **10a** with benzaldehyde and of **10b** (MOMCl, iPr_2NEt, CH_2Cl_2 r.t., 95% from **10a**, $[\alpha]_D$ -59, c=1.1, **m.p.** 73-74°C, ether-heptane) with methacrolein and 3-formylcyclohexenone[8] afforded the B-seco taxane frameworks **5** ($[\alpha]_D$ +8, c=0.8), **11** and **4** ($[\alpha]_D$ -131, c=1.0) in 76, 50, and 55% isolated yield respectively together with recovered starting materials. The C10-C9 bond formation thus achieved set the stage for the A-C-ring linking. Fragmentations were accomplished by lead tetraacetate oxidation ($Pb(OAc)_4$, CH_3CN, -20°, 5 min) either on the α-ketol **12** ($[\alpha]_D$ -21, c=1.0) obtained from **10b** (TBDMSOTf, CH_2Cl_2, collidine, then O_3, CH_2Cl_2-Py, -78°C, and TBAF-THF, 70% combined yield), or its corresponding diol **13** ($NaBH_4$, CH_2Cl_2-EtOH, r.t., 10 min, 98%) leading to the aldehyde-acid **8** or dialdehyde **7** in 98 and 80% yield respectively, ready for further elaboration on C2 and C10.



Setting the C-13 center: With a view to installing the C-13 hydroxy functionality, we studied the nucleophilic epoxidation of enones **16** ($[\alpha]_D$ +118, c=1.0), **18** ($[\alpha]_D$ +46, c=1.3) and **20** ($[\alpha]_D$ +132, c=1.1) prepared from a common precursor, **14** ($[\alpha]_D$ +63, c=1.0, **m.p.** 72-73°C, ether-heptane), in a three step sequence (TMSOTf-collidine, -10°C, 15 min, followed by NBS-THF, -78°C, 10 min and subsequent dehydrobromination with $CaCO_3$-dimethylacetamide, 1 h reflux, 75% overall yield) for the double bond formation, with additional deprotection ($BF_3.Et_2O$, CH_2Cl_2, r.t., quantitative) and Swern oxidation (DMSO, oxalyl chloride, -60°C, 90%) for the enones **16** and **18** (Scheme 1).

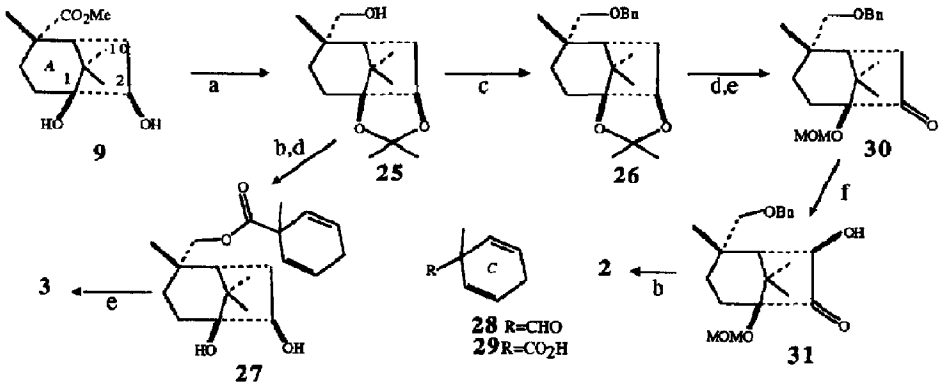


Scheme 1: a) $BF_3.Et_2O$, CH_2Cl_2, r.t. b) TMSOTf-collidine, -10°C, then NBS-THF, -78°C, 10 min., then $CaCO_3$-dimethylacetamide, 1 h reflux c) 30% H_2O_2-6N NaOH, MeOH, r.t. d) DMSO, oxalyl chloride, CH_2Cl_2, -60°C e) 6N NaOH, MeOH, r.t. f) TBDMSOTf, collidine, CH_2Cl_2 g) SmI_2, THF-MeOH, -90°C h) O_3, CH_2Cl_2 , Py, -78°C, then PPh_3.

In the course of this endeavor we discovered a complete facial selectivity reversal from **18** (α-epoxidation, single isomer) to **20** (β-epoxidation, single isomer), while enone **16** gave mixed results (two diastereomers, β/α: 3.5/1) under the same reaction conditions.[9] Thus, tBu-protected enone **20** upon treatment

with 30%-H_2O_2, 6N NaOH, MeOH, at r.t. for 24 h, afforded a 75% yield of β-epoxide **21** ($[\alpha]_D$ +6, c=1.0). Appropriate processing of enone **18** allowed for access to a C-13 α-hydroxylation as required for taxoid A-ring. Stereoselective nucleophilic epoxidation of the latter (NaOH, H_2O_2, MeOH, r.t., 15 min) afforded a 96% yield of α-epoxy ketone **19** ($[\alpha]_D$ +248, c=1.0) which upon room temperature treatment with TBDMSOTf in CH_2Cl_2 in the presence of collidine followed by SmI_2 mediated regioselective epoxide ring opening (3 equiv of SmI_2 in THF-MeOH at -90°C, 15 min) led to aldol **23** (90%, two steps). Ozonolysis (O_3, CH_2Cl_2-Py, -78°C then PPh_3) and subsequent esterification (diazomethane, ether, 0°C), gave **6** (72% from **23**), a conveniently functionalized homochiral A-ring component ready to serve in a "combined strategy " taxoid synthesis. A single step modification of enone **18** (NaOH-MeOH-H_2O, r.t., 2 h) led in a quantitative yield to compound **24** as a result of nucleophilic addition to the non-conjugated carbonyl followed by a ring opening and a double bond migration.

Pre-B-seco taxanes, the "indirection" approach: Attempted aldol type reactions with the hindered aldehyde **28** (ref. 4), having the angular methyl group at C-8, failed.[10] As an alternative sequence we considered the synthesis of target molecules **2** and **3**, containing the left and right half moieties bonded in a way which allows further elaboration towards the taxoid ABC framework, using the same C-C bonding as in the initial strategy. Starting from **9**, acetonide formation (dimethoxy propane, acetone, pTosOH, r.t., 30 min, 98%) followed by reduction (DIBAL-CH_2Cl_2, r.t., 2 h) gave the corresponding alcohol **25** in 99% yield. Esterification with acid **29**, obtained according to ref. 4, (DCC, DMAP, CH_2Cl_2, r.t., 48 h) led to **27** in 90% yield which after a Swern oxidation and MOM-protection (MOMCl, iPr_2NEt, CH_2Cl_2, r.t., 36 h) afforded the desired target molecule **3** ($[\alpha]_D$ -46, c=4.8), in 70% combined yield. Benzyl protection of the alcohol **25** (BnBr, NaH, DMF, r.t., 15 h, 98%) followed by deprotection of the acetonide (2N HCl, THF, r.t., 1.5 h, 96%) and subjection of the resulting diol to the same reaction sequence as for 3, gave compound **30** ($[\alpha]_D$ -20, c=1.0) in 80% overall yield. The latter was transformed by a three-step sequence (TBDMSOTf, Et_3N, CH_2Cl_2, r.t., 2 h, followed by ozonolysis in CH_2Cl_2 at -78°C and subsequent desilylation with TBAF, THF, r.t., 20 min) to the α-ketol **31** ($[\alpha]_D$ -18, c=1.0) in 60% overall yield, which upon esterification with **29** as above gave a 97% yield of **2** [11] ($[\alpha]_D$ -15, c=1.0).



Scheme 2: a) dimethoxy propane, acetone, pTosOH, r.t.,then DIBAL, CH_2Cl_2, r.t. b) **29**, DCC-DMAP, CH_2Cl_2 , r.t. c) BnBr, NaH, DMF, r.t. d) 2N HCl, THF, r.t. e) DMSO-oxalyl chloride, -60°C then MOMCl, iPr_2EtN, CH_2Cl_2 , r.t. f) TBDMSOTf, Et_3N, CH_2Cl_2, r.t., then O_3, CH_2Cl_2 , Py, -78°C, PPh_3.

In conclusion, our route provides a simple entry to several optically homogeneous, multifunctional, left-half taxoid building blocks and allows scope for combined strategies.[12]

References and notes

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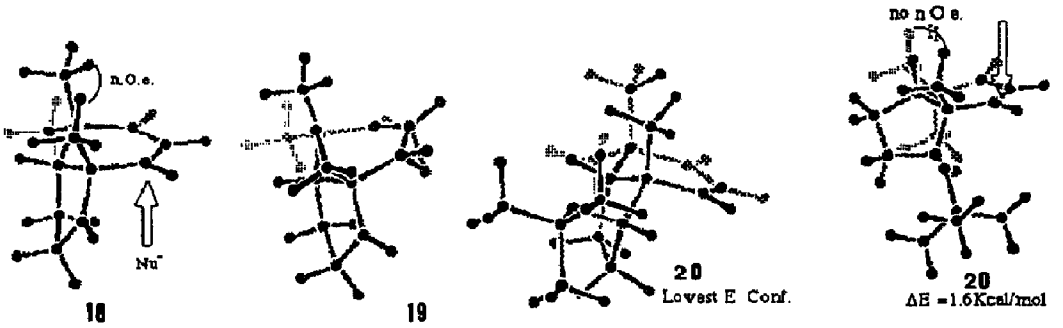
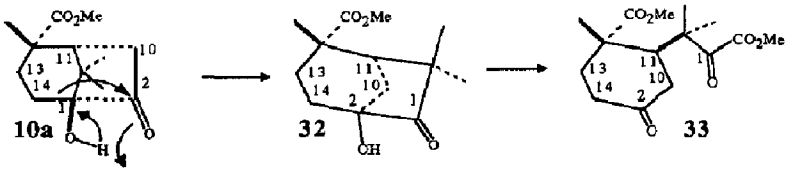
7. High threo selectivity, as expected for cyclic enolates and complete facial selectivity was observed.
8. Quesada, M.L. and Schlessinger, R.H. *Synth. Commun.* **1976**, *6*, 555-557.
9. The facial selectivity reversal can be rationalized using molecular mechanics calculations. The lowest energy conformer **18** accounts well for the stereoelectronically favored α-attack while for the β-face attack the reacting conformer **20** is 1.6 Kcal/mol higher in energy. Conformers derived from MM2 calculations are in agreement with the observed n.O.e.'s.



10. Titanium, cerium or boron enolates proved to be inefficient. On the other hand, heating the α-ketol **10a** in benzene in the presence of a catalytic amount of pTosOH for 4 h initiated an α-ketol rearrangement with C14-C1 bond migration leading to the ketol **32** ($[\alpha]_D$ +52, c=1.0, **m.p.** 86-88°C, pentane-ether) in 72% yield, wich for further characterization was subjected to an oxidative fragmentation ($NaIO_4$, THF-H_2O, 1 h, r.t.) and esterification (CH_2N_2, Et_2O, 0°C) to give **33** ($[\alpha]_D$ +9, c=1.0) in 80% yield.



11. **2**: **I.R.** (film) 3020, 2978, 2930, 2893, 2874, 1763, 1735, 1454, 1267, 1227, 1201, 1155, 1109, 1056, 1037, 994; ^{1}**H-NMR** ($CDCl_3$, 400 MHz) δ 1.09 (3H, s), 1.30 (3H, s), 1.33 (3H,s), 1.34 (3H, s), 1.20-2.30 (5H, m), 2.60 (2H, br.s), 3.19 (1H, d, J=9.0), 3.38 (3H, s), 3.60 (1H, d, J=9.0), 4.37 (1H, d, J=11.8), 4.52 (1H, d, J=11.8), 4.79 (1H, d, J=7.3), 5.23 (1H, d, J=7.3), 5.30 (1H, br.s), 5.65-5.90 (4H, m), 7.30 (5H, m); ^{13}**C-NMR** ($CDCl_3$, 75 MHz) δ 21.9, 25.5, 25.8, 27.0, 29.4, 38.9, 43.8, 52.0, 55.2, 73.0, 73.2, 80.4, 88.3, 92.4, 124.6, 124.8, 127.4, 127.6, 128.2, 138.5, 173.7, 213.7; **EIMS**: 482 ($M^{+\cdot}$, 1), 226(17), 91(100), **CIMS**:.483 ($[M+H]^+$,63), 451(100).
12. Structures for all new compounds were established by high field 1 and 2D NMR techniques and supported by molecular mechanics calculations. Optical rotations were measured in chloroform.

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