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A rapid entry into major groups of taxoids

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Abstract

We report here the construction of **3** to **12**, equipped with functionalization suitable for further elaboration to various taxoids, that demonstrates the validity of our four-step synthesis of the taxoid ABC framework by the transmetallation (C10–C11)-aldol (C1–C2) route.

The ABC core of the taxoid diterpene skeleton still posses challenging synthetic problems despite the impressive number of strategies which have culminated in six complete total syntheses.[1] We had developed an attractive approach[2] that relies on an α-alkoxy stabilized carbanion for the A+C coupling, using the stannylation/destannylation methodology developed by Still[3] and on one of the oldest reactions known in synthesis, the aldol condensation[4] for the central B-ring formation. We now report further elaboration of the tricyclic system **1** which is used as a starting point towards various members of the taxoid family offering practical access into the, hitherto never approached, C12–C13 double bond containing Taxezopidine K **I**, Taxuspine D **II**[5] as well as to the major groups of taxanes, those containing an exocyclic olefin at C4–C20 such as Taxuyunnanine C **III**,[6] a β-epoxide at C4–C20 such as Baccatin I **IV**,[7] and those with an oxetane ring such as Taxol **V** (Scheme 1). With the crucial ABC intermediate, the 12,4(20)-taxadiene **1** in hand, we turned our attention to the more elaborated intermediate **3**, which bears the C-5 α-OH necessary for the corresponding esters and for the C4–C20 epoxide, precursor for the oxetane synthesis and functionality for the C-1 hydroxyl group. The double bonds in **2** can easily be chemodifferentiated; when dienone **2** was subjected to nucleophilic epoxidation, it was clearly evident that the C1–C2 double bond of the dienone system had a much higher reactivity to epoxidation than the C12–C13 double bond. Indeed, when **2** was treated with H_2O_2 and 6N NaOH in methanol at 0°C to room temperature, the epoxy ketone **3** ($[\alpha]_D$ –62, *c* 1.1), that incorporates all carbon atoms of the final taxoid skeleton, was obtained in 91% isolated yield as a single diastereoisomer (Scheme 2).

Next, oxygenation of the C4–C20 olefin, in the presence of the C-5α hydroxyl group, was attempted using standard literature conditions for osmium tetroxide catalyzed dihydroxylation, with a hope for obtaining synthetically useful levels of stereoselection.[8] But, in contrast to the nucleophilic epoxidation,

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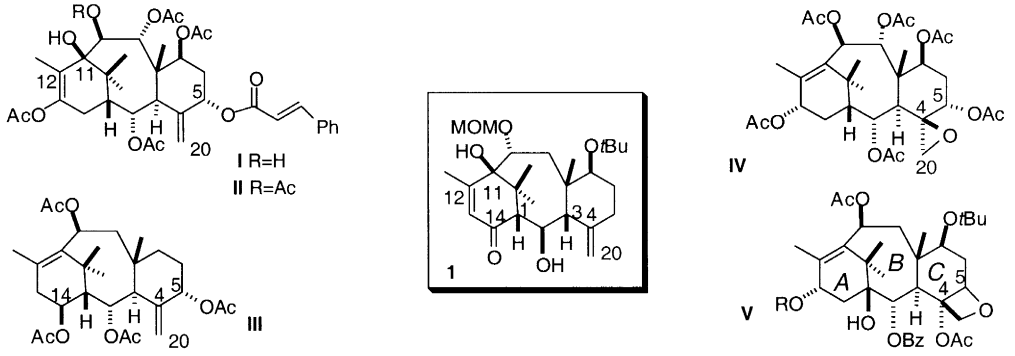
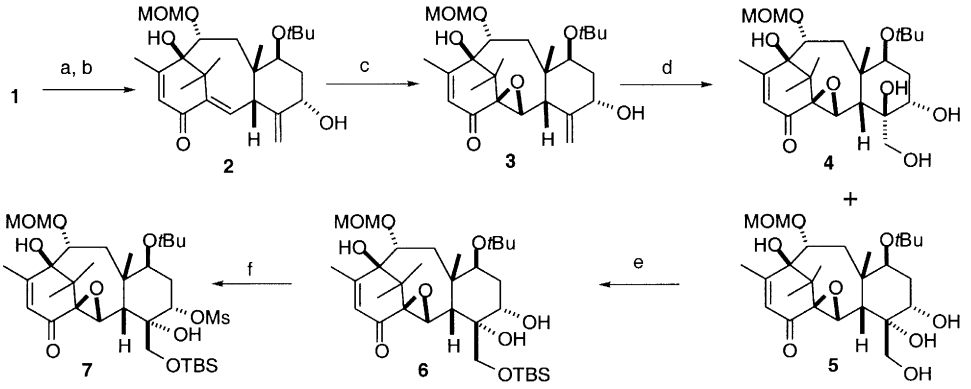


Scheme 1.

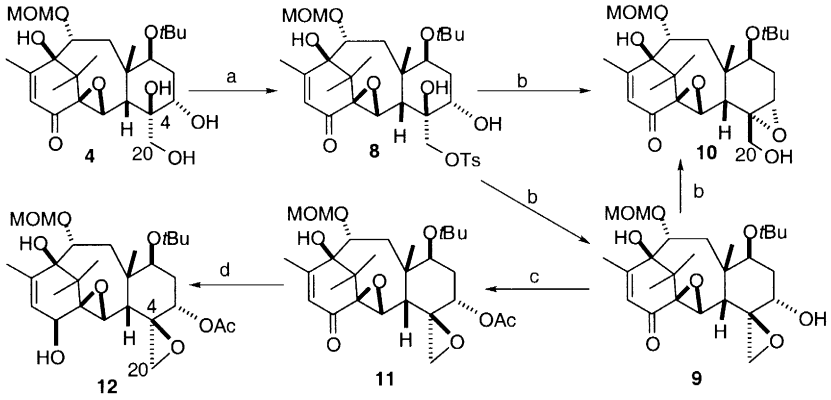
which proceeded exclusively from the β-face of dienone **2** forming the β-epoxide **3**, osmylation (various conditions) of the latter led to a 1.4:1 mixture of triols **4** ($[\alpha]_D$ –63, *c* 2.3) and **5** ($[\alpha]_D$ –55, *c* 1.2) respectively, in 75% combined yield. Protection of triol **5** as its mono-*tert*-butyldimethylsilyl (TBDMS) ether was carried out using standard protocols (TBSCl, Im., DMF, under argon, room temperature, 2.5 h) affording **6** ($[\alpha]_D$ –45, *c* 0.9), in 92% isolated yield. The target C-5 mesylate **7** was then obtained in 88% yield by reacting **6** with MsCl, in dry pyridine, in the presence of cat. DMAP (0°C, 55 min). The synthesis of **7**, a possible direct precursor of oxetane containing taxoids,[9] was therefore achieved in six steps from **1**.



Scheme 2. (a) Ac_2O, Py, DMAP, 0°C then DBU, rt. (b) cat. SeO_2, *t*BuOOH 70% in H_2O, CH_2Cl_2, rt. (c) 30% H_2O_2, 6N NaOH, MeOH, 0°C to rt. (d) OsO_4, NMO, *t*BuOH:H_2O (3:1), Py, rt. (e) TBSCl, Im., DMF, rt. (f) MsCl, Py, DMAP, 0°C

The observed lack of stereoselectivity in the osmium mediated dihydroxylation on tricyclic intermediate **3** allowed a modulable stereoselectivity for the introduction of the C-4 stereocenter. The flexibility of the current method to efficiently introduce and further modify various substituents around the core tricyclic intermediate is demonstrated by the transformations shown in Scheme 3.

The synthetic route that led to the β-C4(20)-epoxy group containing **9**, to the rearranged epoxy alcohol **10** and the C-14 β-OH containing **12** started with the elaboration of triol **4**. Tosylation (TsCl, pyridine, DMAP, 0°C to room temperature) of **4** occurred in high yield, and furnished the required C-20 tosylate **8** ($[\alpha]_D$ −58, *c* 1.4). Subsequent displacement of the tosylate under mild basic conditions proved beneficial; prolonged reaction times resulted in Payne rearrangement leading to **10** ($[\alpha]_D$ −81, *c* 0.5), which reinforces the synthetic utility of the osmylation step. Thus, displacement of the tosylate in **8** under mild conditions (K_2CO_3 in anhydrous methanol at −40°C, 1 h) gave epoxide **9** ($[\alpha]_D$ –66, *c* 1.0), in 98% isolated yield. At longer reaction times, as expected from stereoelectronic considerations,[10] a larger



Scheme 3. (a) TsCl, Py, DMAP, 0°C to rt. (b) K_2CO_3, MeOH. (c) Ac_2O, Py, DMAP, 0°C. (d) $NaBH_4$–$CeCl_3$, EtOH–CH_2Cl_2

predominance of the Payne rearrangement[11] product **10** was observed, until total conversion of **9** to **10**. Finally, conversion of **9** to **12** was achieved via careful acetylation (to avoid the Payne rearrangement product formation) of the bis-epoxy-enone **9**, successfully carried out at 0°C in dry pyridine using Ac_2O and DMAP as catalyst. Subsequent reduction of **11** thus obtained with sodium borohydride in the presence of $CeCl_3$ in ethanol–methylene chloride (1:1, at −25°C, 40 min) gave the alcohol **12** as a single stereomer in 98% isolated yield.[12] The β-OH stereochemistry at C-14 and the β-disposition of the epoxy functionality at C4(20) were supported by the observation of diagnostic NOEs involving Me-17, Me-19 and H-14, H-2, H-20 protons.

The route followed is operationally simple and serves to further validate the synthetic utility of our A+C strategy. The synthetic scheme described herein represents one of the most straightforward routes to these compounds. The oxetane D-ring construction is deferred to the end of the synthetic scheme, and so is the C-3 stereochemistry. Complete IR, mass, ^1H and ^{13}C NMR data were obtained for each compound synthesized; optical rotations were measured in chloroform.

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12. Compound **12**: $[\alpha]_D$ –3 (*c* 1.21). IR (film): 3493, 2974, 1739, 1462, 1372, 1234, 1190, 1078, 1031, 949, 916, 866, 738, 702, 675 cm^{-1}. ^1H NMR (800 MHz): 1.02 (3H, s, Me-16), 1.16 (9H, s, *t*Bu), 1.22 (3H, s, Me-19), 1.41 (3H, s, Me-17), 1.61 (1H, d, *J*=12.4, H-3), 1.74 (1H, dd, *J*=7.2, 16.0, H-9α), 1.88 (3H, d, *J*=1.3, Me-18), 1.95 (1H, d, *J*=16.0, H-9β), 1.99 (1H, td, *J*=3.4, 14.9, H-6α), 2.08 (3H, s, MeCO), 2.16 (1H, ddd, *J*=3.3, 11.7, 14.9, H-6β), 2.71 (1H, d, *J*=4.8, H-20), 2,81 (1H, d, *J*=4.8, H-20), 3.19 (1H, d, *J*=12.4, H-2), 3.43 (3H, s, OMe), 3.68 (1H, dd, *J*=3.4, 11.7, H-7), 3.72–3.73 (1H, m, H-14), 3.84 (1H, s, OH), 3.94 (1H, d, *J*=7.2, H-10), 4.63 (1H, br.s, H-5), 4.65 (1H, d, *J*=6.9), 4.75 (1H, d, *J*=6.9), 5.84–5.86 (1H, m, H-13). ^{13}C NMR (200 MHz): 17.4 (Me-19), 19.6 (Me-18), 19.7 (Me-16), 21.3 (*Me*CO), 27.1 (Me-17), 28.8 (3C, *t*Bu), 33.0 (C-6), 40.0 (Cq-15), 40.5 (C-9), 40.8 (Cq-8), 47.2 (C-3), 49.4 (C-20), 55.2 (Cq-4), 55.9 (MeO), 64.8 (Cq-1), 67.0 (C-2), 68.3 (C-7), 73.8 (Cq–*t*Bu), 74.7 (C-14), 75.6 (C-5), 76.7 (C-10), 80.8 (Cq-11), 94.3 (-OCH_2O-), 124.2 (C-13), 141.4 (Cq-12), 169.2 (Me*CO*). CIMS: 525 ($[MH]^+$, 5), 449 (3), 435 (16), 405 (19), 389 (79), 271 (38), 253 (48), 153 (100), 135 (69), 121 (37), 95 (50). HRCIMS: calcd for $C_{28}H_{45}O_9$ *m/z* 525.3063, found 525.3069.