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Benzobicyclo[8.4.0.^{1,6}0^{8,13}]tetradecenones: Ring CD-Taxoid Models by Planar Tether Controlled Cycloaddition

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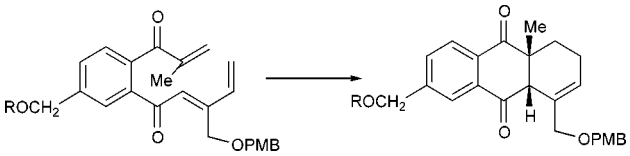
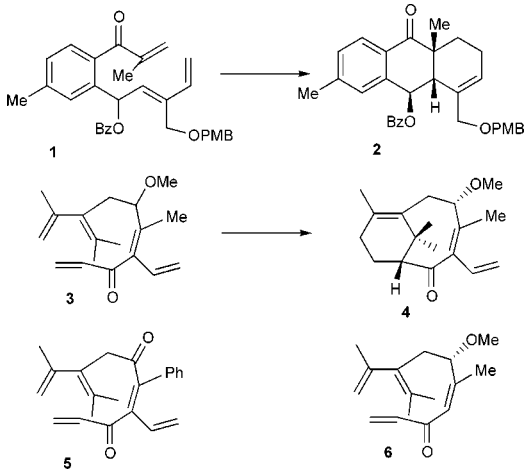
ABSTRACT



A general approach to functionalized hexahydroanthracene dione skeletons is described. The planar dicarbonyl triene 15 cyclized spotaneously upon oxidation of the precursor diol 14 to the tricyclicdiketone 16. The adducts 16 and 2 were further transformed to the corresponding epoxides and oxetanes as a model for the D ring of taxoids.

The ability to control the facial selectivity and develop mild reactions for intramolecular Diels−Alder reactions is of paramount importance in synthetic applications. Motivated in part by our interest in the synthesis of taxoids,[1] we have established that planar "tether control groups" (aromatic rings, *cis* double bonds) in the side chain have a dramatic influence on the ease of cyclization of substituted trienes in intramolecular Diels−Alder cycloadditions.[2] In the case of the conversion of **1** to **2** it appeared that the nonbonded interaction between the benzoate and the PMB group helped control the stereochemistry of the adduct. However, as discussed below this is not the dominant effect. More recently these principles, using a *cis* alkene, have been employed for a direct synthesis of the AB taxane ring system (**3** to **4**).[3] However, the key features for a successful cycloaddition are quite subtle, as neither **5** nor **6**[4] cyclized, and the success of the cyclization requires the conformational bias introduced by the presence of both the endo and exo double bonds and the adjacent methyl group. Consequently for this bicyclo-

Scheme 1



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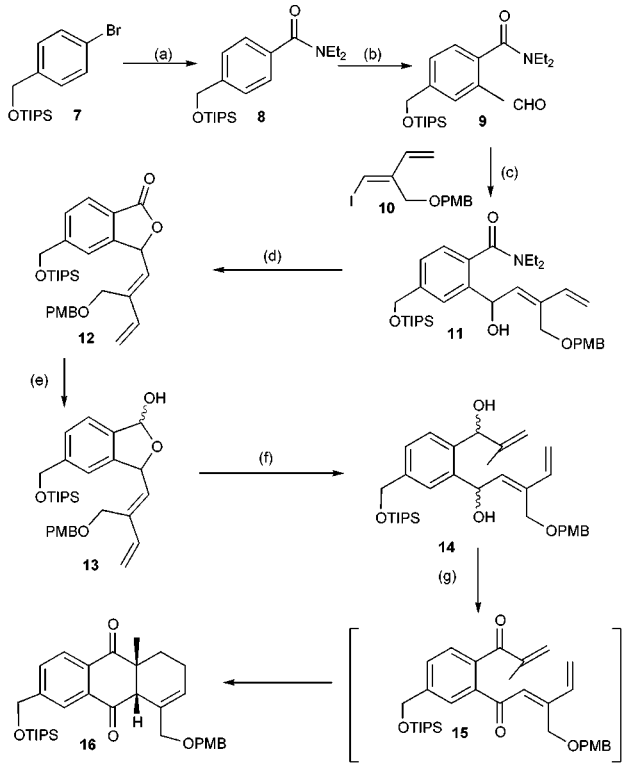
[5.3.1]undecene ring system a flat enedione conjugated system is deleterious as the result of an unfavorable combination of geometric and electronic effects. However, as described below, with the correct substitution pattern flat, fully conjugated aromatic systems can be employed. These tricyclic systems have been converted to epoxides and oxetanes as a model study for our taxane syntheses.

4-Bromobenzyl alcohol was protected as its triisopropylsilyl ether to provide **7** (Scheme 2). The diethyl amide was

Scheme 2[a]

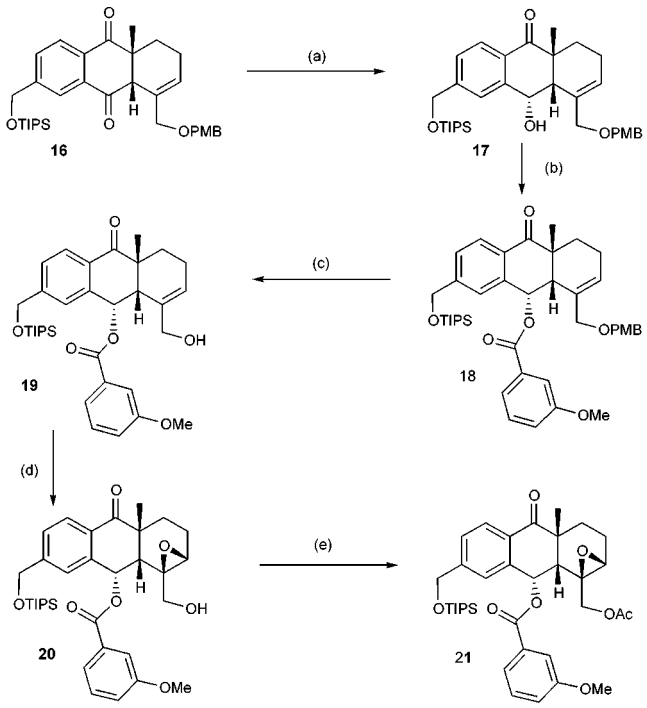


[a] (a) *s*-BuLi, THF, −78 °C, $ClCONEt_2$, −78 °C, 0.5 h, 68%; (b) *s*-BuLi, 15 min, DMF, −78 to 21 °C, 88%; (c) iododiene **10**, *s*-BuLi, −78 °C, 15 min, 85%; (d) 5 equiv *p*-TsOH, THF, 15 °C, 3 h, 70%; (e) DIBALH, toluene, −78 °C, 3 h, 93%; (f) isopropenylmagnesium bromide, THF, 0 °C, 1 h, 88%; (g) IBX, DMSO, 21 °C, 15 h, 55%.

introduced into the para position by quenching the anion derived from metal−halogen exchange with *sec*-butyllithium with the acyl chloride to afford **8**. In the next step the diethyl amide moiety controlled the directed *ortho*-metalation under standard conditions[5] (−78 °C, THF, TMEDA, *s*-BuLi then DMF, 88%) to provide the aldehyde **9**. The requisite iododiene **10** was prepared by carbometalation of 3-trimethylsilylpropargyl alcohol as described previously.[6] Halogen exchange mediated by *s*-BuLi and condensation with the aldehyde **9** generated the diene-alcohol **11** in 85% yield. Initially, under various conditions, clean hydrolysis of the amide proved troublesome when the secondary hydroxyl was first protected as an ether. However, acid-catalyzed hydrolysis at 15 °C with *p*-toluenesulfonic acid resulted in the formation of the lactone **12** directly. The corresponding lactol **13** was generated in 93% yield upon exposure to diisobutylaluminum hydride. Subsequent addition of isopropenylmagnesium bromide to the hemiacetal afforded the triene-diol **14** as a 1:1 mixture of diastereomers. The oxidation of this diol was initially examined with Dess−Martin periodinane,[7] but the acidity of this reagent resulted in partial removal of the silyl protecting group. The use of the neutral precursor oxidant IBX (1-hydroxy-1,2-benziodol-3(1*H*)-one 1-oxide)[8] in DMSO avoided this complication and provided the tricyclic dicarbonyl adduct **16** directly via **15** in 55% yield. (This represents a yield >80% for each step). This adduct is the *cis* fused product that arises from an endo transition state and indicates that additional stereochemical interactions are not required to achieve this selectivity.

Selective reduction of the less hindered ketone in **16** was accomplished with the bulky reducing agent *tert*-butoxy aluminum hydride, which delivered the hydride from the top face to provide **17** as a single diastereomer (Scheme 3). NOE

Scheme 3[a]



[a] (a) LiAl(*t*-OBu)$_3$H, 2-methyl-2-propanol, C_6H_6, 80 °C, 2.5 h, 60%; (b) 3-MeO−BzCl, Et_3N, DMAP, 21 °C, 1.5 h, 90%; (c) DDQ, CH_2Cl_2/H_2O, 18:1, 21 °C, 1.5 h, 72%; (d) *m*-ClPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 1.5 h, 90%; (e) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 21 °C, 2 h, 90%.

measurements confirmed that the hydroxyl group was *anti* to the methyl group and the bridgehead hydrogen. The

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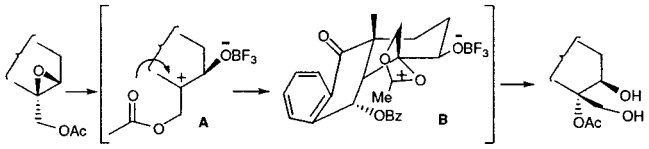
alcohol was esterified upon reaction with 3-methoxybenzoyl chloride in dichloromethane containing 4-(dimethylamino)-pyridine and triethylamine to form the benzoate **18**. Oxidative removal of the *p*-methoxybenzyl group was effected with dichlorodicyanoquinone to afford the primary alcohol **19**. Epoxidation of the allylic alcohol with *m*-chloroperoxybenzoic acid gave the epoxide **20** as a single isomer consistent with attack from the top face. The requisite primary acetate **21** was prepared under standard conditions (DMAP, Et_3N) with acetic anhydride in 90% yield. This set the stage to examine the ring opening rearrangement sequence to the acetoxy diol, described initially by Coxon,[9] Berkowitz,[10] and their co-workers.

Their unsubstituted cyclohexane model lacked the stereochemical features of **21** but demonstrated that in the absence of constraints the acetoxy-diol product should be formed with inversion of configuration of the tertiary hydroxyl center. Thus it was anticipated that in the case of **21** the developing carbocation **A** would be captured from the bottom face to form the acetoxonium ion **B** (Scheme 4). Unfortunately and

Scheme 4

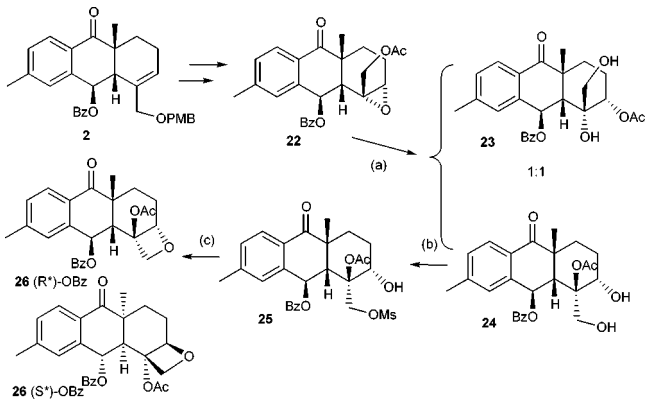


unexpectedly, the epoxide **21** was inert to various Lewis acid mediated reaction conditions. The failure to attain the anticipated intermediate appeared to be a consequence of the steric inhibition created by the presence of the axial benzoate substituent

In the Diels−Alder adduct **2**, prepared earlier,[2] the benzoate occupies the epimeric equatorial position, and thus the rational for the failure of the rearrangement of **21** was confirmed by the following series of experiments.

A parallel epoxidation sequence on the primary alcohol derived from **2** afforded the epoxy-acetate **22** (Scheme 5). This structure was confirmed by X-ray analysis and established that the epoxide and the axial benzoate possessed a *trans* relationship. This orientation is the inverse of **21**, as a result of the steric hindrance provided by the *cis* substituents on the top face. Exposure of this epoxide to borontrifluoride

Scheme 5[a]



[a] (a) $BF_3{\cdot}OEt_2$, NaOAc, CH_2Cl_2, −78 to −5 °C, 1 h, 42%; (b) MsCl, NEt_3, DMAP, 21 °C, 62%; (c) DBU, MeC_6H_5, 105 °C, 1.5 h, 61%.

etherate at low temperature (−78 to −5 °C) generated a 1:1 mixture of **23** and **24** from which the desired diastereomer **24** was separated by chromatography. The lack of stereochemical discrimination confirmed the analysis above and also emphasized the difficulty of predicting the anticipated product in these series. Mitsunobu conditions did not provide the oxetane **26**, but selective activation of the primary alcohol as its mesylate **25** allowed facile ring closure to the oxetane **26** upon exposure to DBU in toluene at 105 °C.[11] The oxetane is racemic and thus has been redrawn [(**26** (*S**)-OBz] to reflect the relationship with the taxoids, in which the relative stereochemistry of the benzoate, bridgehead hydrogen, and oxetane is correct, although the angular methyl group has the opposite orientation (epimeric) in the natural series.

In conclusion, we have established that, contrary to some of our initial experiments, relatively flat trienes afford intramolecular adducts with appropriate stereocontrol. In addition, the stereochemical subtleties of the epoxide-rearrangement sequence to the acetoxy-oxetane moiety present in taxanes have been delineated.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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