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ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-α-2,7,11-CEMBRATRIENE-4,6-DIOL (α-CBT)

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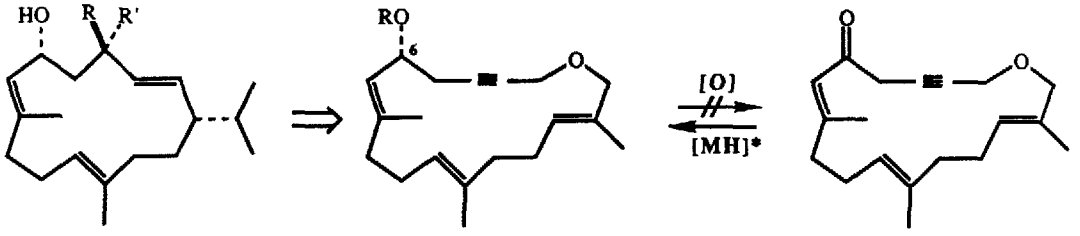
Summary: The total synthesis of (+)-α-CBT (16) was effected from the achiral 17-membered ketone 3 by a sequence featuring asymmetric reduction, diastereoselective [2,3] Wittig ring contraction and hydroxyl directed epoxidation as stereochemically important steps.

The diastereomeric tobacco cembranes α- and β-CBT[1] (I and II) have been shown to inhibit both plant growth[2] and tumor promotion.[3] We recently reported a total synthesis of the racemic β-isomer II by a route featuring a novel diastereoselective [2,3] Wittig ring contraction of the 17-membered propargylic ether III.[4] The present study was undertaken to develop a stereorational synthesis of α-CBT that would define both the relative and absolute stereochemistry of the natural product.



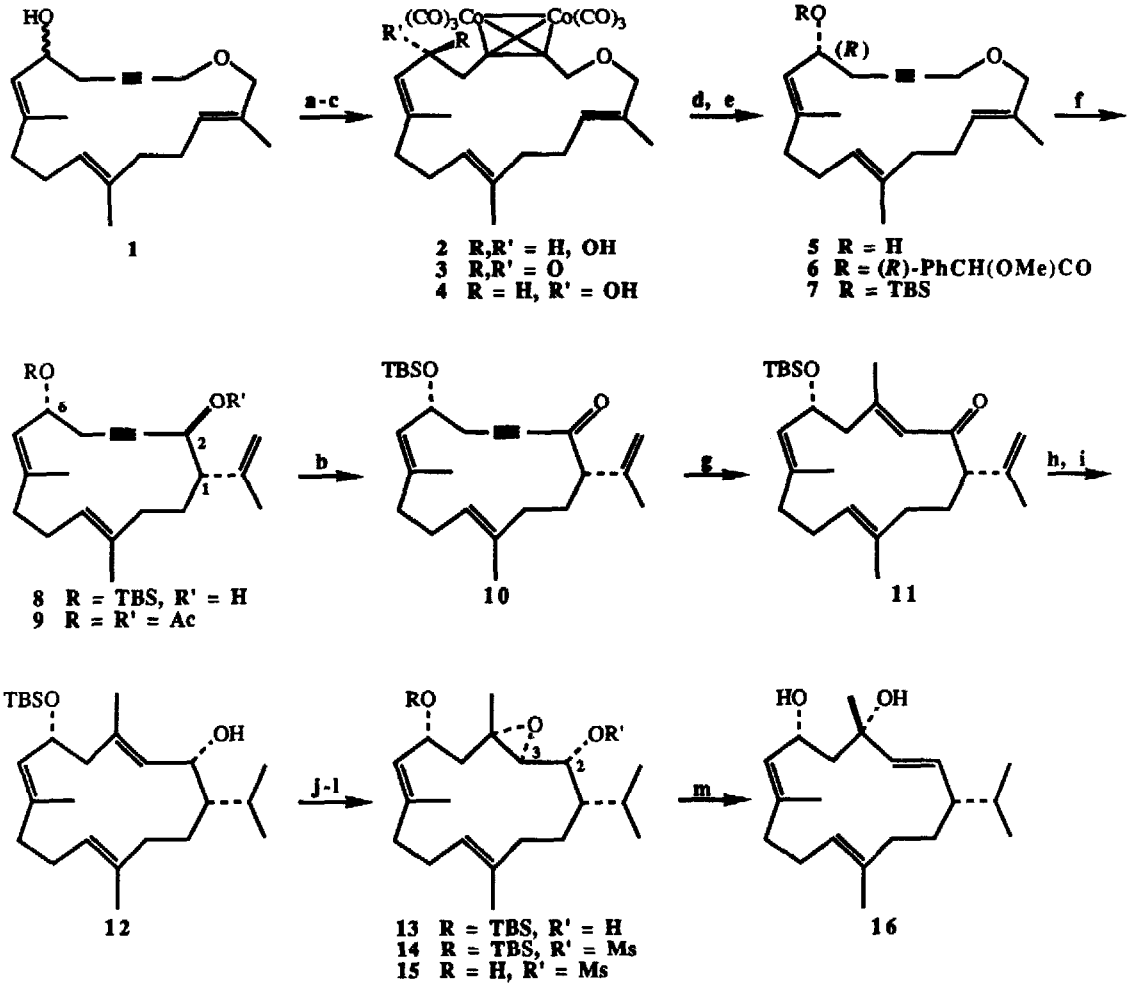
I R = Me, R' = OH
II R = OH, R' = Me

III

IV

We have previously shown that a bulky alkoxyl substituent at C6 of the macrocyclic ether III exerts considerable conformational control on the [2,3] Wittig ring contraction leading to a marked preference for the *trans,syn* diastereoisomer (*cf.* 7 → 8).[4] It was of interest to prepare this ether in a configurationally defined manner and employ the resulting scalemic[5] rearrangement product 8 for the synthesis of natural α-CBT or its enantiomer.

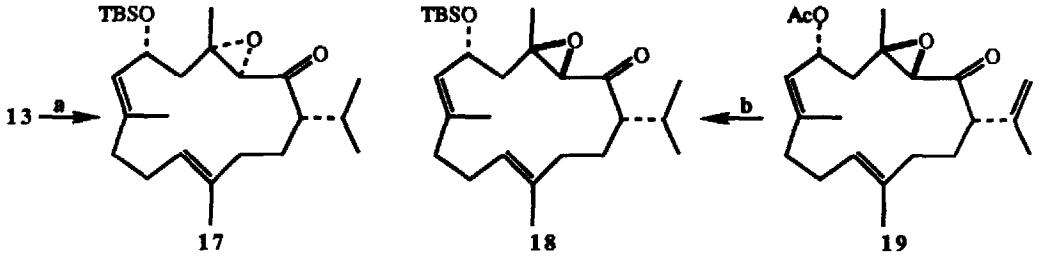
In line with configurational assignments established for other tobacco derived cembranoids,[6] we selected the *R* enantiomer for initial study. We had hoped to prepare the (*R*)-alcohol 5 by asymmetric reduction of the propargyl ketone IV, but all attempts at oxidation of the racemic alcohol (III, R = H) led to the conjugated allenic ketone instead. In order to circumvent the apparently facile alkyne-allene isomerization we turned to the Co complex 2, readily prepared by treatment of racemic alcohol 1 with $Co_2(CO)_8$ in ether.[7] Oxidation by the Swern protocol[8] afforded ketone 3 which was reduced to the Co-complexed homopropargylic alcohol 4 with the $LiAlH_4$-Darvon alcohol ("Chirald®") complex.[9] Treatment of 4 with ceric ammonium nitrate led to the desired alcohol 5 of 71% ee whose configuration was assigned through ^1H NMR analysis of the (*R*)-O-methyl mandelate 6 as previously described for related compounds.[10]



(a) $Co_2(CO)_8$, Et_2O (98%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (83%); (c) Chirald-$LiAlH_4$, Et_2O, -78°C; (d) $(NH_4)_2Ce(NO_3)_6$, MeOH, Et_2O, (90%, two steps); (e) TBSCl, Et_3N, DMAP, CH_2Cl_2 (89%); (f) *n*-BuLi-TMEDA, THF, pentane, -78°C (85%); (g) Me_2CuLi, Et_2O, 0°C (90%); (h) DIBAH, THF, -78°C (96%); (i) $(Ph_3P)_3RhCl$, H_2, C_6H_6, EtOH (69%); (j) $VO(acac)_2$, *t*-BuOOH, $PhCH_3$ (88%); (k) CH_3SO_2Cl, C_5H_5N, CH_2Cl_2, 0°C (92%); (l) Bu_4NF, THF (92%); (m) Na, NH_3, THF, -40°C (75%)

[2,3] Wittig ring contraction of the TBS ether **7** was effected with *n*-BuLi • TMEDA affording a 73:11:16 mixture of the *trans,syn*:*trans,anti*:*cis,syn* diastereoisomers[11] favoring the *trans,syn* isomer **8**.[4] Swern oxidation[8] of this mixture gave ketone **10** as a 90:10 mixture of syn and anti isomers. Addition of Me_2CuLi yielded the (*E*)-enone **11** also as a 90:10 syn:anti mixture plus a small amount (<10%) of the isomeric (*Z*)-isomer(s).[4] This mixture was reduced with $(i\text{-Bu})_2AlH$ and selectively hydrogenated with Wilkinson's catalyst[12] affording alcohol **12** in 69% yield after separation from isomeric impurities by column chromatography.

Epoxidation of allylic alcohol **12** with $VO(acac)_2$, *t*-BuOOH afforded a single epoxide **13**. The epoxide stereochemistry was confirmed through conversion to the keto epoxide **17** which was isomeric with the diastereomer **18** derived from **19**, a substance whose structure was previously determined, as the racemate, by x-ray analysis.[4]



(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) K_2CO_3, MeOH; TBSCl, Et_3N, DMAP, CH_2Cl_2; $(Ph_3P)_3RhCl$, C_6H_6, EtOH, H_2

The final steps of the sequence were effected along lines of our β-CBT synthesis.[4] Thus epoxy alcohol **13** was converted to epoxy mesylate **15** through treatment with methanesulfonyl chloride in pyridine and desilylation. The observed H2/H3 coupling of 9.6 Hz is suggestive of a favored anti arrangement for this epoxy mesylate. Reductive elimination with sodium ammonia afforded the (*E*) allylic diol **16**, $[\alpha]_D$ +90°, identical according to ^1H, ^{13}C NMR and TLC comparison with an authentic sample. The ee of this material was calculated as 73% by ^{19}F NMR analysis of the Mosher ester derivative. Since the rotation of the synthetic and natural material is of the same sign and comparable magnitude, correcting for ee, the absolute configuration of α-CBT can be assigned as 1*S*,4*S*,6*R* (**16**).

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13. Roberts and Rowland report $[\alpha]_D$ +281.6° for α-CBT. We obtained a value of +173° on a crystalline sample kindly provided by Dr. Y. Saito, Japan Tobacco Inc.

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