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Synthesis of the Otteliones A and B: Use of a Cyclopropyl Group as Both a Steric Shield and a Vinyl Equivalent**

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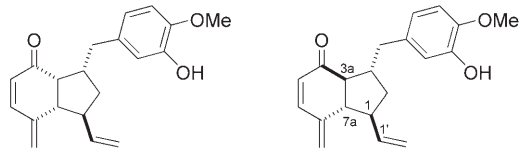
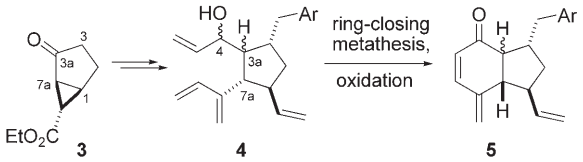
The otteliones A (**1**) and B (**2**),[1–3] are exceptionally potent anticancer agents that inhibit the growth of a wide range of tumor cell lines with in vitro GI_{50} values of less than 100 pM for **1** and less than 1 nM for **2**.[1] For example, total growth inhibition was observed against one breast cancer cell line and one CNS cancer cell line in the nM to pM range. [1] Additionally, it has been established that ottelione A inhibits tubulin polymerization.[3] Both compounds are clearly important because of this impressive biological activity and their unusual structures.[4]



(+)-ottelione A (**1**) (-)-ottelione B (**2**)

Two syntheses of **1** and **2** have been reported,[5,6] and these established the absolute configurations. Both routes used an isomerization of **1** to gain access to **2**.[7] In the first synthesis[5] it was stated that treatment of **1** with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in hot benzene gave **2** in 83% yield with an $[\alpha]_D$ of −250 ($c = 0.24$, $CHCl_3$). Attempts to apply this DBU method in the second synthesis[6] gave a 1:1 mixture of the otteliones. When eventually *t*BuOK was used, a 23:77 mixture (79% yield) of **1** and **2** was produced, from which separation by HPLC on a chiral stationary phase gave **2** in 23% yield with an $[\alpha]_D$ of −333 ($c = 0.18$, $CHCl_3$). The isomerization process is clearly not straightforward, and we describe here a route that avoids this problem.

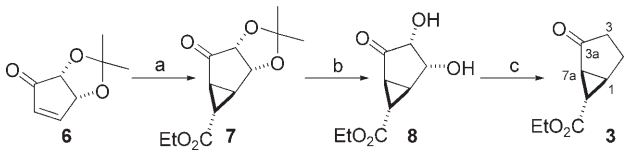
The essential features of our approach are summarized in Scheme 1. The ring-closing-metathesis steps (**4**→**5**) require a high degree of regioselectivity among several double bonds, and this critical point was tested by first making the racemic core structures of both otteliones,[8] and then the racemic otteliones themselves.[9]



3 **4** **5**

Scheme 1. Key features of the synthesis.

For the optically pure series, the precursor **3** satisfied all our requirements and was readily available by asymmetric cyclopropanation of 2-cyclopentenone[10] or by elaboration of D-ribose. We have used both approaches, but for most of our study we employed the carbohydrate. Methyl 2,3-*O*-isopropylidene-D-ribofuranosides[11] were converted in five steps into the cyclopentenone **6** as reported.[12]. Cyclopentanone **6** then underwent cyclopropanation (Scheme 2, **6**→**7**) on treatment with $EtO_2CCH_2S^+Me_2 \cdot Br^-$ and DBU.[13] Acidic hydrolysis liberated the diol **8**, and its conversion into **3** was then achieved by dimesylation (MsCl, Et_3N) and hydrogenation/hydrogenolysis[14] in the presence of Et_3N.



6 **7** **8** **3**

Scheme 2. Reagents and conditions: a) $Me_2S^+CH_2CO_2Et\ Br^-$, DBU, 92%; b) aq HCl/THF, 88%; c) MsCl, Et_3N; Pd/C, *i*Pr_2NEt, H_2, 57%. Ms = methanesulfonyl.

Condensation of the enolate derived from **3** with 4-methoxy-3-(*tert*-butyldimethylsiloxy)benzaldehyde (**9**),[15] gave the epimeric alcohols **10** (Scheme 3), and removal of the hydroxy group was achieved by the action of Et_3SiH in the presence of $BF_3 \cdot Et_2O$[16] so as to complete the attachment of the $ArCH_2$ group with the rigorous stereochemical control exerted by the shape of the ketone **3**. Simple alkylation of **3** gives a much lower yield than our two-step method. At this point, reduction of **11** with $LiAlH_4$ generated diol **12**.[17] The primary hydroxy group of **12** was acylated with *t*BuCOCl and the secondary hydroxy group was oxidized. The stage was now set for the cyclopropyl unit to discharge its last function by serving as a precursor to the C(1) vinyl group; this it did in a very satisfactory way on treatment with freshly-prepared SmI_2,[19,20] and ketone **14** was isolated in 82% yield. Although *trans* 2,4-disubstituted cyclopentanones are thermodynami-

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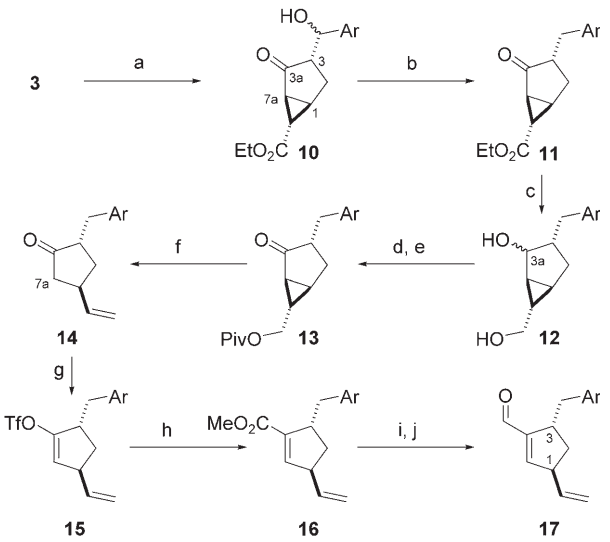


Scheme 3. Reagents and conditions: a) LDA, THF, −78 °C, 1 h, 4-methoxy-3-(*tert*-butyldimethylsiloxy)benzaldehyde (**9**), 91 %; b) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 1 h, 87 %; c) $LiAlH_4$, THF, 0 °C, to RT, 4 h; d) *t*BuCOCl, pyridine, THF, 0 °C, 1 h, RT, 30 min; e) DMP, CH_2Cl_2, RT, 1 h, 77 % from **11**; f) SmI_2, MeOH, THF, 0 °C, 5 h, 82 %; g) KHMDS, THF, −78 °C, 1 h, Comins reagent, 2 h, 92 %; h) $Pd(OAc)_2$, Ph_3P, Et_3N, MeOH, CO, DMF, 24 h, 77 %; i) DIBAL, CH_2Cl_2, −78 °C, 1 h; j) DMP, CH_2Cl_2, 45 min, 93 % overall. DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, DMP = Dess–Martin periodinane, KHMDS = potassium 1,1,1,3,3,3-hexamethyldisilazide, LDA = lithium diisopropylamide, Piv = pivaloyl, Tf = trifluoromethanesulfonyl.

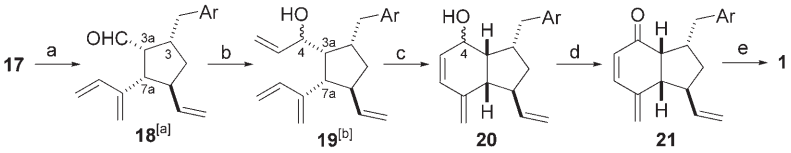
cally less stable than the corresponding *cis* isomers,[20] the product formed by the present route was exclusively *trans*; attempts to introduce the vinyl group by conjugate addition to a cyclopentenone gave poor stereoselectivity.

The next task was to introduce a butadienyl group at the C7a position, and in preparation, ketone **14** was converted into enol triflate **15** by quenching the derived kinetic enolate with the Comins reagent.[21] Carbonylation in the presence of MeOH[22] then afforded ester **16**, which was converted into aldehyde **17** by reduction with DIBAL and Dess–Martin oxidation. Aldehyde **17** is an advanced key intermediate as it allows the introduction of the butadienyl group as well as divergence of the route to either ottelione.

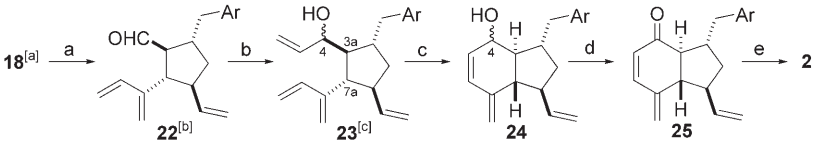
Conjugate addition of a butadien-2-yl cuprate[23–25] to **17** occurred exclusively *trans* to the vinyl group at the C1 position (Scheme 4), and protonation of the resulting enolate occurred mainly (> 7:1) from the face opposite the C3 substituent to give aldehyde **18**. This compound was used directly for reaction with vinylmagnesium bromide to form **19** (69 %) as a mixture of two alcohols, which were epimeric only at the C4 position. Ring-closing metathesis with the Grubbs I catalyst bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (5 mol %) afforded the dienes **20** in almost identical yield (91–93 %) from either epimeric alcohol. Evidently, the reaction proceeds with very high, and perhaps complete, selectivity among the double bonds.[8,26] Oxidation to **21** was straightforward, and pure **1** ($[\alpha]_D = 19.7$; $c = 0.28$, $CHCl_3$) was then reached by removal of the silyl protecting group on the aromatic ring with Bu_4NF in CH_2Cl_2 (0 °C, 10 min); the *cis* stereochemistry at the ring fusion was not compromised when this step was carried out under the indicated conditions.

Our route to ottelione B was also based on aldehyde **18**. Treatment of the aldehyde with DBU at room temperature afforded a mixture of the C3a isomers that was mainly the desired *trans* compound **22** (> 10:1 *trans*/*cis*; Scheme 5). Reaction of this mixture with vinylmagnesium bromide gave the alcohols **23** (88 %), epimeric only at C4. These tetraenes underwent efficient and regioselective ring-closing metathesis to give the desired alcohols **24**. Once again, the synthesis was completed by Dess–Martin oxidation and desilylation with Bu_4NF; the product **2** had an $[\alpha]_D$ of −331.4 ($c = 0.18$, $CHCl_3$).

We were unable to crystallize ottelione A, but did obtain crystals of ottelione B that were suitable for X-ray analysis. The X-ray data show that the six-membered ring is in a half-chair conformation, and that the vinyl group is oriented in such a way that the hydrogen atoms at the C1′ and C7a positions are *syn* to each other, with both of the C–H bonds parallel. The dihedral angle between the carbonyl group and the C3a–H bond is around 114°.



Scheme 4. [a] 60 % yield of a mixture, > 7:1 in favor of the indicated 3a,7a-*cis* stereochemistry. [b] Epimeric only at C4. Reagents and conditions: a) 1. 2-chloro-1,3-butadiene, Mg, $ZnCl_2$, THF/toluene, reflux, 1 h; 2. −78 °C, $CuBr{\cdot}SMe_2$, HMPA, Me_3SiCl, 3. CF_3CO_2H, 0 °C; b) vinylmagnesium bromide, THF, 0 °C, 45 min, 69 %; c) 5 mol % Grubbs I cat., CH_2Cl_2, RT, 24 h, 91–93 %; d) DMP, mixure of C4 epimers of **20**, CH_2Cl_2, 1 h, 91 %; e) Bu_4NF, CH_2Cl_2, 0 °C, 10 min, 84 %. HMPA = hexamethyl phosphoramide.



Scheme 5. [a] > 7:1 in favor of 3a,7a-*cis* stereochemistry. [b] > 10:1 in favor of indicated stereochemistry. [c] Epimeric only at C4. Reagents and conditions: a) DBU, CH_2Cl_2, RT, 36 h, 91 %; b) vinylmagnesium bromide, THF, 0 °C, 1 h, 88 %; c) 10 mol % Grubbs I cat., CH_2Cl_2, RT, 20 h, 86 %; d) DMP, mixture of C4 epimers of **24**, CH_2Cl_2, 1 h, 93 %; e) Bu_4NF, CH_2Cl_2, 0 °C, 10 min, 87 %.

Our synthetic route demonstrates a high degree of selectivity between several double bonds in the ring-closing metathesis and the ability of a cyclopropane ring to first exert a steric effect and then to provide a vinyl substituent. The

successful operation of each of these factors allowed access to either ottelione.

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