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Total Synthesis of *epi*-Otteliones

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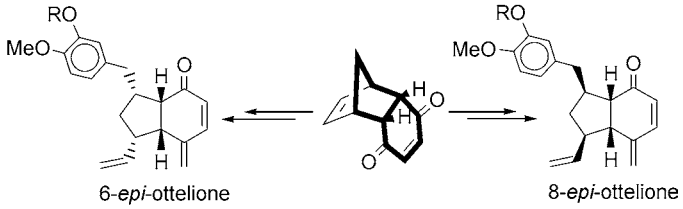
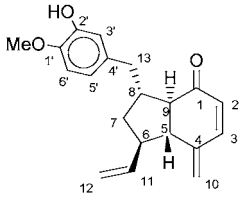
ABSTRACT



Syntheses of 6-*epi*- and 8-*epi*-otteliones, corresponding to earlier proposed structures of the biologically potent natural product ottelione A, have been accomplished from the readily available Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone.

Otteliones A and B are two recently isolated novel natural products from the widely occurring freshwater plant *Ottelia alismoides*, which lines irrigation canals and rice fields in southeast Asia and Africa.[1] The plant and its constituents have engaged attention in view of the recent reports emanating from China that its extract in clinical trials cured two cases of bilateral tuberculosis of cervical lymph gland within 3 months.[2] Structures of otteliones were investigated in a collaborative effort between Egyptian and US scientists employing high-field NMR and modeling studies and led to the formulation **1** for ottelione B, but the structure of ottelione A could not be gleaned unambiguously.[1] Ottelione A was formulated as having either structure **2a** or **3a** with preference for the former.[1] The presence of an unusual 4-methylene-cyclohex-2-enone substructure[3] in otteliones and their impressive biological activity profile, exhibiting antitubercular activity and cytotoxicity at nM−pM levels against a panel of 60 human cancer cell lines at the National Cancer Institute, attracted the attention of many synthetic chemists.[1,2b,4] As the structure of ottelione A was shrouded in some uncertainty,



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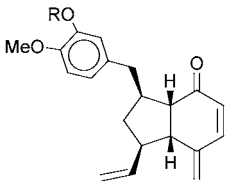
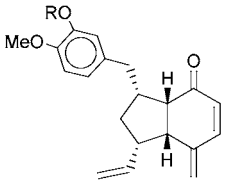
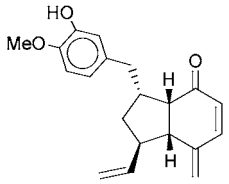


2a. R=H
2b. R=isopropyl



3a. R=H
3b. R=isopropyl



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total synthesis of these promising natural products was considered as an objective that would not only resolve the structural ambiguity but also provide access to other diastereomers for biological evaluation. We therefore initiated in late 1998 synthetic studies directed toward the projected

(1) Ayyad, S. E. N.; Judd, A. S.; Shier, W. T.; Hoye, T. R. *J. Org. Chem.* **1998**, *63*, 8102.

(2) (a) Li, H.; Li, H.; Qu, X.; Shi, Y.; Guo, L.; Yuan, Z. *Zhongguo Zhongyao Zazhi* (*Chin. J. Chin. Mater. Med.*), **1995**, *20*, 115, 128. (b) Leboul, J.; Prevost, J. French Patent WO96/00205, 1996; *Chem. Abstr.* **1996**, *124*, 242296.

(3) This electrophilic functionality has rarely been reported in the literature, and its role in promoting biological responses could be promising but remains unexplored; see: (a) Murray, D. F.; Baum, M. W.; Jones, M. *J. Org. Chem.* **1986**, *51*, 1. (b) Jung, M. E.; Rayle, H. L. *Synth. Commun.* **1994**, *24*, 197. (c) Wild, H. *J. Org. Chem.* **1994**, *59*, 2748.

(4) (a) Mehta, G.; Reddy, D. S. *Chem. Commun.* **1999**, 2193. (b) Mehta, G.; Islam, K. *Synlett* **2000**, 1473. For other approaches to otteliones, see: Trembleau, L.; Patiny, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 6377.

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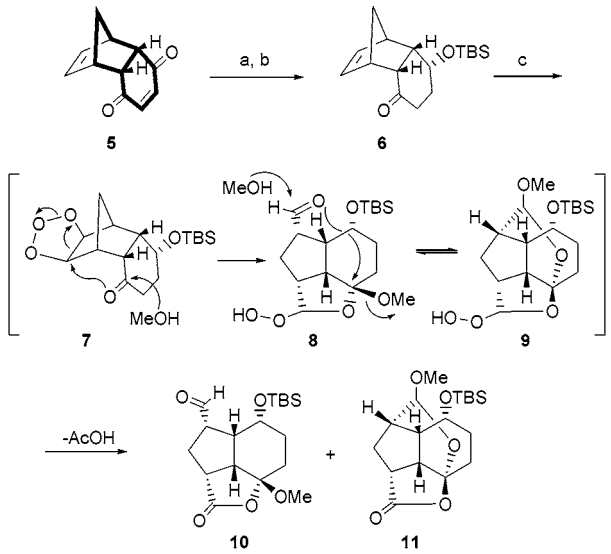
structures **2a** and **3a**.[4a,b] During the course of these studies a group at Rhone−Poulenc Rorer (now Aventis) in France, while evaluating the mechanism of anticancer activity of ottelione A, proposed an alternate structure **4** for the natural product in 2000.[5] Structure **4** for the natural product has now been firmly confirmed through our recent total synthesis.[6] However, our initial travails toward the earlier formulations **2a** and **3a** of ottelione A has resulted in the total synthesis of epimeric ottelione derivatives **2b** and **3b**, making these new substrates available for biological screening, and these efforts form the subject matter of this letter.

Our approach to otteliones was pivoted around the recognition that the requisite cis-hydrindane skeleton (see bold lines) is embedded within the readily available endo-tricyclic Diels−Alder adduct **5** of cyclopentadiene and *p*-benzoquinone.[7] Additionally, the required stereochemical features at all four stereogenic centers are clearly discernible in **5**. Stereoselective LAH reduction of **5** and protection of the *endo*-hydroxyl group led to **6**, Scheme 1. Unsymmetrical

Scheme 1[a]



[a] Reagents and conditions: (a) $LiAlH_4$, ether, 0 °C, 78%. (b) TBDMSCl, Imz, DCM, 85%. (c) (i) O_3, DCM−MeOH, −78 °C; (ii) Ac_2O, Et_3N, DCM, rt (**10** = 45%, **11** = 18%).

ozonolysis[8] of **6**, under conditions that lead to terminally differentiated products, was regioselective and resulted in lactones **10** (45%)[9,10] and **11** (18%),[9,10] whose stereostructures were secured through single-crystal X-ray structure determination (Figures 1 and 2).[10] A possible explanation for the regioselectivity observed during unsymmetrical ozonolysis and leading to the formation of **10** and **11** could be in terms of assisted intramolecular cleavage of the molozonide as in **7** followed by intervention of intermediates **8** and **9**, respectively, Scheme 1.

Chemoselective addition of the organolithium reagent derived from isopropyl-protected 5-bromo-2-methoxyphenol **12**[11] to the aldehyde group in the major lactone **10** led to the keto-lactone **13**, as a single diastereomer, Scheme 2. Chemoselective DIBALH reduction of the lactone moiety

(5) Combeau, C.; Provost, J.; Lanceli, F.; Tournoux, Y.; Prod'homme, F.; Herman, F.; Lavelle, F.; Leboul, J.; Vuilhorgne, M. *Mol. Pharm.* **2000**, *57*, 553.

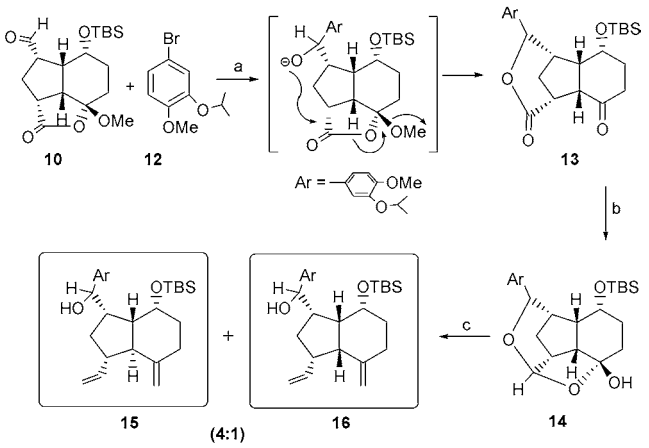
(6) Mehta, G.; Islam, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2396.

(7) Diels, O.; Blom, J. M.; Koll, W. *Ann.* **1925**, *443*, 247. (b) Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J. *J. Chem. Soc.* **1964**, 3062.

(8) (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (b) Taber, D. F.; Nakajima, K. *J. Org. Chem.* **2001**, *66*, 2515.

(9) All compounds reported here are racemic and were fully characterized on the basis of spectroscopic (IR, ^1H and ^{13}C NMR, mass) data and elemental analyses. **Selected Spectral Data. 14**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (1H, s), 6.99 (1H, dd, J = 1.8, 8.4 Hz), 6.8 (1H, d, J = 8.1 Hz), 5.77 (1H, d, J = 6.9 Hz), 5.32 (1H, s), 4.57 (1H, m), 4.17 (1H, m), 3.83 (3H, s), 3.13 (1H, m), 2.46 (1H, m), 2.36 (3H, m), 2.14 (2H, m), 1.98−1.78 (2H, m), 1.34 (6H, m), 1.25 (1H, m), 0.89 (9H, s), 0.16 (3H, s), 0.08 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ149.6 (q), 146.86 (q), 136.81 (q), 119.81 (CH), 114.57 (CH), 111.69 (CH), 104.39 (q), 104.09 (CH), 73.09 (CH), 71.72 (CH), 70.84 (CH), 56.01 (OCH_3), 48.16 (CH), 45.13 (CH), 45.0 (CH), 44.83 (CH), 34.49 (CH_2), 30.65 (CH_2), 25.97 (3 CH_3), 24.88 (CH_2), 22.27 (CH_3), 22.04 (CH_3), 18.35 (q), −4.6 (CH_3), −4.82 (CH_3); MS *m*/*z* 490 (M^+). **15**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (1H, s), 6.89 (1H, d, J = 8.4 Hz), 6.82 (1H, d, J = 8.7 Hz), 5.87 (1H, m), 5.08−4.97 (3H, m), 4.74 (1H, s), 4.70 (1H, s), 4.61 (1H, bs), 4.56 (1H, m), 3.99 (1H, m), 3.83 (3H, s), 2.49−2.32 (4H, m), 2.08 (2H, m), 1.86−1.69 (3H, m), 1.52 (1H, m), 1.36 (6H, d, J = 6.0 Hz), 0.99 (9H, s), 0.23 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.03 (q), 148.97 (q), 146.85 (q), 142.40 (CH), 136.07 (q), 118.48 (CH), 114.40 (CH), 113.95 (CH_2), 111.69 (CH), 104.67 (CH_2), 71.37 (CH), 71.19 (CH), 69.68 (CH), 56.08 (OCH_3), 54.75 (CH), 47.07 (CH), 45.04 (CH), 44.96 (CH), 36.54 (CH_2), 31.02 (CH_2), 30.43 (CH_2), 26.25 (3 CH_3), 22.17 (CH_3), 22.09 (CH_3), 18.55 (q), −3.85 (CH_3), −4.03 (CH_3); MS *m*/*z* 486 (M^+). **16**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, s), 6.96 (1H, dd, J = 1.8, 8.4 Hz), 6.84 (1H, d, J = 8.1 Hz), 6.08 (1H, m), 4.93−4.86 (2H, m), 4.83 (1H, s), 4.74 (1H, s), 4.59 (1H, bs), 4.54 (1H, m), 3.99 (1H, bs), 3.85 (3H, s), 2.87 (2H, m), 2.45 (1H, m), 2.27−1.96 (5H, m), 1.8 (1H, dd, J = 4.2, 14.1 Hz), 1.36 (6H, d, J = 6.3 Hz), 1.26−1.19 (2H, m), 1.0 (9H, s), 0.24 (3H, s), 0.17 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.13 (q), 147.64 (q), 147.30 (q), 141.53 (CH), 137.05 (q), 119.47 (CH), 114.67 (CH), 113.42 (CH_2), 111.88 (CH), 110.10 (CH_2), 74.32 (CH), 71.52 (CH), 67.77 (CH), 55.99 (OCH_3), 51.03 (CH), 49.21 (CH), 47.75 (CH), 47.17 (CH), 35.16 (CH_2), 33.26 (CH_2), 27.96 (CH_2), 26.46 (3 CH_3), 22.16 (2 CH_3), 18.55 (q), −3.49 (CH_3), −4.55 (CH_3); MS *m*/*z* 486 (M^+). **18**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (3H, m), 5.72 (1H, m), 4.93 (3H, m), 4.80 (1H, s), 4.49 (1H, m), 3.82 (3H, s), 3.24 (1H, t, J = 9.0 Hz), 3.11 (1H, q, J = 6.6 Hz), 2.82 (2H, m), 2.66 (1H, dd, J = 8.7, 13.2 Hz), 2.53 (2H, m), 2.44−2.18 (3H, m), 1.97 (1H, m), 1.62 (1H, m), 1.34 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.62 (CO), 148.66 (q), 147.03 (q), 144.44 (q), 139.81 (CH), 134.67 (q), 121.05 (CH), 116.91 (CH), 114.42 (CH_2), 113.21 (CH_2), 112.12 (CH), 71.36 (CH), 56.06 (OCH_3), 54.92 (CH), 53.02 (CH), 46.77 (CH), 45.58 (CH), 41.75 (CH_2), 36.47 (CH_2), 36.22 (CH_2), 33.74 (CH_2), 22.16 (CH_3), 22.11 (CH_3); MS *m*/*z* 354 (M^+). **21**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (3H, m), 5.60 (1H, m), 4.92 (3H, m), 4.81 (1H, s), 4.52 (1H, m), 3.82 (3H, s), 2.98 (1H, m), 2.62 (2H, m), 2.58−2.36 (6H, m), 2.23 (1H, m), 2.02 (1H, m), 1.35 (6H, m), 1.17 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.05 (CO), 148.72 (q), 146.96 (q), 144.3 (q), 140.14 (CH), 133.03 (q), 121.45 (CH), 116.86 (CH), 114.85 (CH_2), 112.09 (CH_2), 111.84 (CH), 71.31 (CH), 57.92 (OCH_3), 55.99 (CH), 54.25 (CH), 47.89 (CH), 41.75 (CH_2), 41.52 (CH_2), 38.39 (CH), 37.77 (CH_2), 30.78 (CH_2), 22.16 (CH_3), 22.09 (CH_3); MS *m*/*z* 354 (M^+). **3b**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (1H, d, J = 9.9 Hz), 6.85 (1H, s), 6.79 (2H, s), 5.89 (1H, d, J = 9.9 Hz), 5.53 (1H, m), 5.38 (1H, s), 5.24 (1H, s), 4.86 (1H, s), 4.81 (1H, d, J = 7.5 Hz), 4.51 (1H, m), 3.82 (3H, s), 3.32 (1H, m), 3.27 (1H, m), 2.85 (1H, m), 2.76 (1H, m), 2.71 (1H, m), 2.25 (1H, m), 2.01 (1H, m), 1.35 (6H, m), 1.25 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.59 (CO), 148.5 (q), 146.94 (q), 146.83 (CH), 141.45 (q), 139.89 (CH), 135.10 (q), 129.28 (CH), 121.18 (CH_2), 121.10 (CH), 117.04 (CH), 114.79 (CH_2), 112.02 (CH), 71.29 (CH), 56.06 (OCH_3), 50.50 (CH), 47.93 (CH), 47.21 (CH), 47.13 (CH), 36.86 (CH_2), 36.50 (CH_2), 22.16 (CH_3), 22.11 (CH_3); MS *m*/*z* 352 (M^+). **2b**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (1H, d, J = 9.9 Hz), 6.82 (1H, s), 6.77 (2H, s), 5.91 (1H, d, J = 9.9 Hz), 5.63 (1H, m), 5.37 (1H, s), 5.20 (1H, s), 5.01 (1H, d, J = 10.5 Hz), 4.87 (1H, d, J = 17.4 Hz), 4.54 (1H, m), 3.82 (3H, s), 2.97 (1H, m), 2.81 (1H, m), 2.73 (1H, m), 2.64−2.57 (2H, m), 2.24 (1H, m), 1.98 (1H, m), 1.36 (6H, d, J = 5.7 Hz), 1.21 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.85 (CO), 148.9 (q), 147.11 (q), 145.61 (CH), 140.65 (q), 140.45 (CH), 133.05 (q), 126.5 (CH), 121.61 (CH_2), 121.55 (CH), 117.09 (CH), 115.89 (CH_2), 112.01 (CH), 71.42 (CH), 56.06 (OCH_3), 53.76 (CH), 50.14 (CH), 48.74 (CH), 41.96 (CH_2), 41.14 (CH), 37.51 (CH_2), 22.21 (CH_3), 22.14 (CH_3); MS *m*/*z* 352 (M^+).

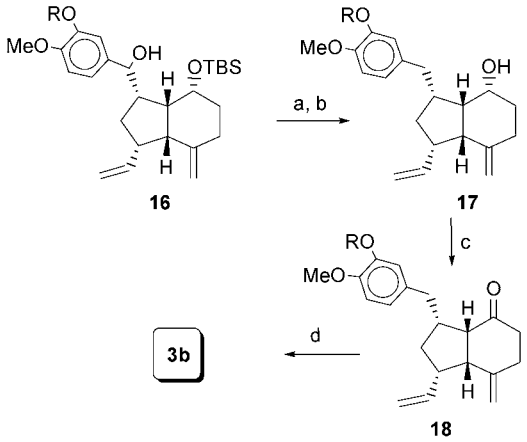
Scheme 2[a]



[a] Reagents and conditions: (a) ^{n}BuLi, THF, −78 °C, 71%; (b) DIBALH, DCM, −78 °C, 68%; (c) PPh_3CH_3I, *t*BuOK, benzene, rt, 84%.

in **13** resulted in the formation of bis-acetal **14** with two masked carbonyl groups locked internally. Twofold Wittig olefination in **14** installed both the vinyl and terminal methylene groups and led to diastereomeric diolefins **15** and **16** (4:1), the former predominating.[9] While the minor diolefin **16** was the expected *cis*-hydrindane, the major product was a *trans*-hydrindane **15** formed through ring junction epimerization during the Wittig reaction, Scheme 2.[12] Since the minor product **16** had maintained its stereochemical integrity[13] during the Wittig reaction, it was elaborated to ottelione **3b**. Reductive deoxygenation of the benzylic hydroxl group in the metal−ammonia milieu and removal of the TBS protective group in **16** led smoothly to **17**, Scheme 3. PCC oxidation in **17** furnished ketone **18**.[9] The stage was now set for the generation of the sensitive 4-methylenecyclohex-2-enone substructure present in otteliones, and this was accomplished by executing the phenylselenation−selenoxide elimination sequence in **18** to furnish **3b**, Scheme 3. An incisive analysis of the NMR spectra of **3b** indicated that its spectral features were distinctly different from the natural ottelione A **4** and it had an 6-*epi*-ottelione A structure.[9]

Scheme 3[a]



[a] Reagents and conditions: (a) Li, liq NH_3, THF, −33 °C, 73%. (b) TBAF, THF, 65 °C, 88%. (c) PCC, DCM, 0 °C, 96%. (d) (i) LiHMDS, PhSeCl, THF, −78 °C; (ii) 30% H_2O_2, DCM, 0 °C, 68%.

(10) **Crystal Data for Compound 10.** The structure was solved by direct methods (SIR92). Refinement was made by full-matrix least-squares procedures on F2 using SHELXL-97. Crystal system, monoclinic; space group, *P*2(1)/*c*. Cell parameters, $a = 13.3204$ (3) Å, $b = 14.0856$ (4) Å, $c = 11.0632$ (3) Å, $\beta = 104.842$ (1)°, $V = 2006.49$ (9) Å^3, $Z = 4$, ρ(calcd) = 1.174 g/cm^3, $F(000) = 768.0$, $\mu = 0.139$ cm^{-1}, $\lambda = 0.71$ Å. $R_1 = 0.0613$ for $F_o > 2\sigma(F_o)$ and 0.0892 for all data. GOF = $S = 1.013$.

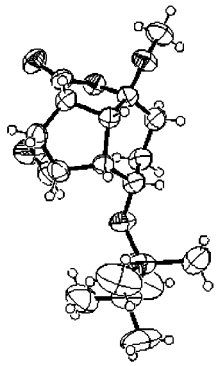


Fig. 1. ORTEP of compound 10

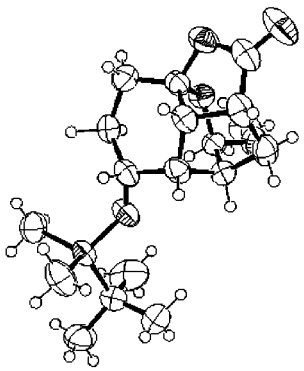


Fig. 2. ORTEP of compound **11**

Crystal Data for Compound 11. The structure was solved by direct methods (SIR92). Refinement was made by full-matrix least-squares procedures on F2 using SHELXL-97. Crystal system, monoclinic; space group, *P*2(1)/*c*. Cell parameters, $a = 14.084$ (2) Å, $b = 11.505$ (2) Å, $c = 12.279$ (2) Å, $\beta = 98.799$ (3)°, $V = 1966.34$ (12) Å^3, $Z = 4$, ρ(calcd) = 1.198 g/cm^3, $F(000) = 768.0$, $\mu = 0.14$ cm^{-1}, $\lambda = 0.71$ Å. $R_1 = 0.0547$ for 2789 $F_o > 4\sigma(F_o)$ and 0.0832 for all 4081 data. GOF = $S = 0.972$, restrained GOF = 0.972 for all data. **Crystal Data for *p*-Nitrobenzoate Derivative of Compound 19.** The structure was solved by direct methods (SIR92). Refinement was made by full-matrix least-squares procedures on F^2 using SHELXL-97. The compound was crystallized from a hexane−dichloromethane solvent system. It has been observed that a hexane molecule also crystallized with the compound. Crystal system, triclinic; space group, *P*-1. Cell parameters, $a = 11.379$ (8) Å, $b = 11.880$ (8) Å, $c = 13.365$ (10) Å, $\alpha = 108.458$ (12)°, $\beta = 107.445$ (13)°, $\gamma = 103.048$ (13)°, $V = 1528.93$ Å^3, $Z = 2$, ρ(calcd) = 1.098 g/cm^3, $F(000) = 540.0$, $\mu = 0.08$ mm^{-1}, $\lambda = 0.71073$ Å. $R_1 = 0.1042$ for 1947 $F_o > 4\sigma(F_o)$ and 0.2258 for all 5198 data. GOF = $S = 0.917$, restrained GOF = 0.917 for all data. An ORTEP drawing (excluding the hexane molecule for clarity) with 50% ellipsoidal probability is shown below.

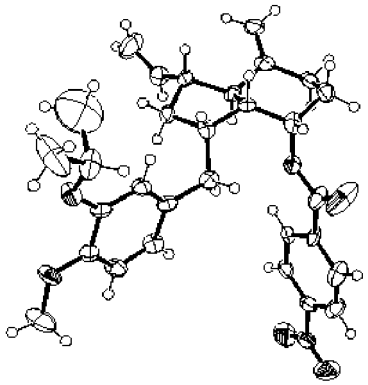
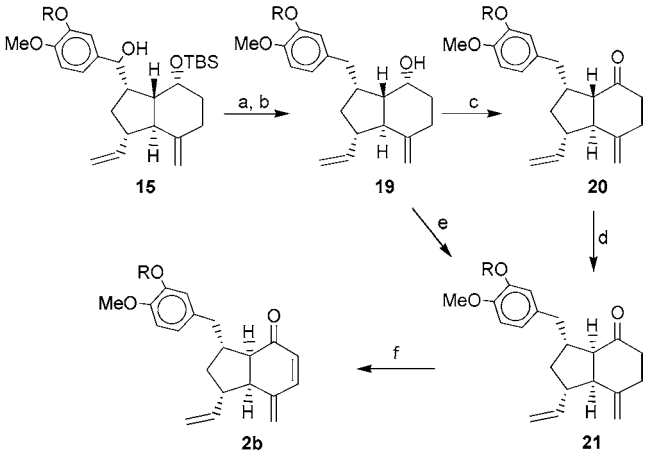


Fig. 3. ORTEP of *p*-nitrobenzoate derivative of **19**.

(11) Conde, J. J.; Mendelson, W. *Tetrahedron Lett.* **2000**, *41*, 811.

Attention was next turned to the major Wittig product, the *trans*-hydrindane **15**, which through unanticipated but productive steps was elaborated to the 8-*epi*-ottelione structure **2b**, corresponding to the previously favored[1] stereostructure of the natural ottelione A. Metal−ammonia reductive deoxygenation in **15** and TBS deprotection led to trans hydroxy compound **19**, Scheme 4. An X-ray crystal

Scheme 4[a]



[a] Reagents and conditions: (a) Li, liq NH_3, THF, −33 °C, 84%. (b) TBAF, THF, 65 °C, 88%. (c) PCC, DCM, 0 °C, 92%. (d) DBU, C_6H_6, 70 °C, 95%. (e) IBX, C_6H_6, 70 °C, 65%. (f) (i) LHMDS, PhSeCl, THF, −78 °C; (ii) 30% H_2O_2, DCM, 0 °C, 71%.

structure (Figure 3) at this stage of the *p*-nitrobenzoate derivative of **19** fully secured its structure as well as that of the precursor Wittig product **15**.[10] PCC oxidation of **19** furnished the bicyclic ketone **20** in good yield, and to our surprise, we found that when it was exposed to the base DBU, epimerzation occurred to furnish the *cis*-ketone **21**. Indeed, when hydroxy compound **19** was oxidized with IBX, a reagent known to promote enolization,[14] epimerized ketone **21** was directly realized, Scheme 4. It is interesting to note that during the double-Wittig olefination on **14**, base-catalyzed epimerization of *cis*-hydrindane **14** to the *trans*-hydrindane **15** was encountered (Scheme 2), while in the case of *trans*-hydrindane **20**, epimerization to the cis isomer **21** was observed, Scheme 4. Calculation (AM1 level) of heats of formation for **20** ($\Delta H_f = -77.59$ Kcal/mol) and **21** ($\Delta H_f = -84.59$ Kcal/mol) indicated that the latter is about 7 Kcal/mol more stable than the former. Thus, relocation of the carbonyl group (cf. **13** and **20**) and its repositioning vis-à-vis other groups on the hydrindane frame can profoundly affect the cis vs trans isomer stability in this system. Indeed, in evolving from *cis*-**14** to *cis*-**21**, both the hydrindane ring junctions had been sequentially inverted. Thus, access to *cis*-ketone **21** was a very desirable outcome as the stereochemistry at the four stereogenic centers in it corresponded exactly to that present in the then favored structure **2a** of ottelione A. Consequently, **21** was subjected to a phenylselenation−selenoxide elimination sequence to deliver **2b**, Scheme 4. However, the NMR spectral data of **2b** was once again at variance with that of the natural product **4**, clearly implying the need for the revision of the stereostructure of the natural product, which was subsequently achieved both through the reinterpretation[5] of the spectral data and through total synthesis.[6]

In conclusion, we have delineated a short and novel approach to 8-*epi*- and 6-*epi*-ottelione A derivatives **2b** and **3b**, respectively, corresponding to previously assigned structures **2a** and **3a**, respectively, for the natural product, from the readily available Diels−Alder adduct of cyclopentadiene and *p*-benzoquinone. In the process, we have unconvered some interesting stereochemical features and reactivity patterns exhibited by the hydrindane ring system. Besides furnishing new diastereomers of the biologically active natural product, our synthetic studies set the stage for the revision of the structure of ottelione A **4** and its eventual total synthesis.[5,6]

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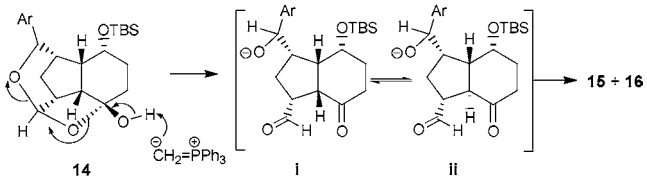
(12) Ylide-mediated bisacetal opening in **14** leads to intermediate **i** in which bridgehead isomerization to **ii** takes place. Interestingly, the stereochemistry of the *endo*-aldehyde group remains secured during the Wittig reaction conditions.



(13) Upon ozonolysis, **16** reverts back to **14** through intramolecular cascade acetalization, thus securing the *cis*-hydrindane stereochemistry and the integrity of the *endo*-vinyl group.

(14) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.