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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 5305–5307

A short synthetic route to the core structures of otteliones A and B

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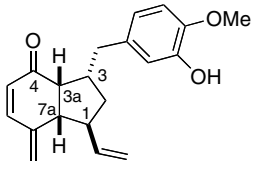
Received 8 May 2005; accepted 7 June 2005

Abstract—Conjugate addition of the cuprate derived from 2-lithio-2,3-butadiene to 1-cylopentenecarbaldehyde, reaction with vinylmagnesium bromide, ring closing metathesis, and oxidation gives the cis-ring fused core of the anticancer agent ottelione A. Epimerization of the initial conjugate addition product and application of the same reactions as used for the ottelione A core, give the trans-ring fused core of ottelione B.

Ottelione A (**1**)[1–3] and ottelione B (**2**)[1] are notably powerful antitumor agents isolated in small amounts (each 0.0009% of dry weight)[1] from a fresh water plant called *Ottelia alismoides* whose native range is east Asia and southeast Asia to Australia.[4] Ottelione A shows GI_{50} values (50% growth inhibition) against many tumor cell lines of <100 pm,[1–3] while ottelione B was found to have GI_{50} values of <1 nm.[1] Total growth inhibition was observed against several cell lines, again in the pm to nm range.[1] Ottelione A is an inhibitor of tubulin polymerization.[3] The structures of the two compounds were deduced[1–3] from very detailed NMR analyses but, while the relative stereochemistry of ottelione B was fully assigned,[1] that for ottelione A[1,3] had to await total synthesis[5] before a firm decision could be made.



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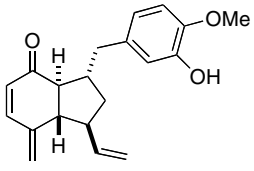

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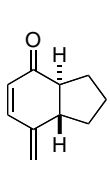
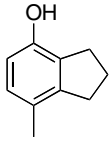


3

Several years ago, work was begun in this laboratory on the synthesis of ottelione B. At that time it was felt that it would be advisable to begin by making the core structure **3** so as to evaluate its properties, the expectations being, of course, that the compound might be sensitive to isomerization to the indane **4**, and that an examination of the properties of **3** would be helpful in any attempt at total synthesis of the actual natural product.



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Although those early experiments[6] did indeed lead to **3**, it so happened that immediately after submitting the work for publication, a paper by Mehta and Islam appeared[5] in which the first route to (±)-ottelione B was described. Key features of that route were formation of (±)-ottelione A and the finding that the compound could be isomerized efficiently to the trans isomer (ottelione B). In the light of this publication, it did not seem appropriate to continue our own studies. Several months later, the same authors,[7] and also Katoh and co-workers,[8] independently described syntheses of optically active natural otteliones A and B; both approaches were again based on the cis→trans isomerization of ottelione A (Scheme 1).[9] Mehta and Islam[7] carried out this crucial step by using DBU in PhH at 65 °C. Katoh and co-workers found[8] (at least in their preliminary experiments) that under these conditions a 1:1 mixture of the two otteliones is formed; they were, however, able to effect isomerization using *t*-BuOK in *t*-BuOH, although isolation of the desired product from the resulting 23:77

Keywords: Ottelione A; Ottelione B; Ring closing metathesis; Synthesis; Core structure; Anticancer activity.
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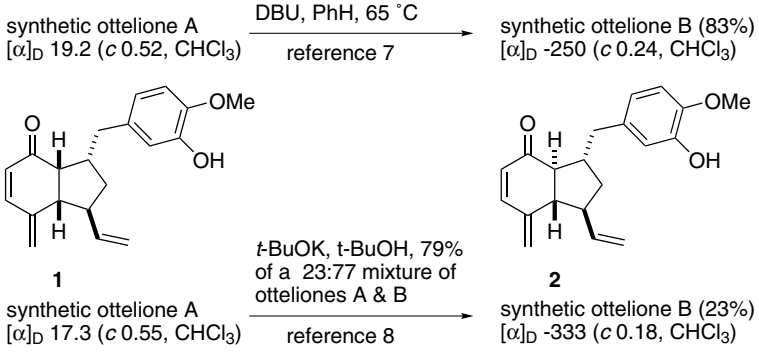
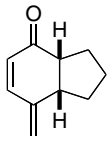
doi:10.1016/j.tetlet.2005.06.021



Scheme 1.

ottelione A/ottelione B mixture required HPLC separation. It would appear that the cis→trans isomerization is not straightforward, and so further synthetic work on the otteliones can be justified, especially in view of their exceptional anticancer[1–3] potency. Therefore, we have taken up this project again and report here a simple method for making the two core structures **3** and **5**. The cis isomer **5** was prepared first.

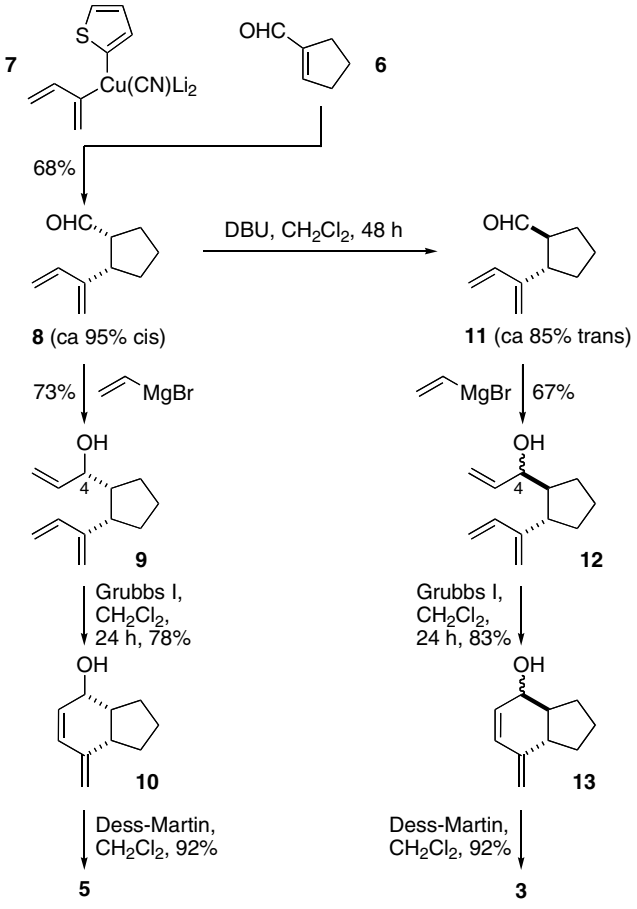
Our route begins with the readily available[10] aldehyde **6**. The compound was subjected to conjugate addition with the organocuprate **7**, itself prepared from lithium 2-thienylcyanocuprate (THF solution) and 2-lithio-1,3-butadiene, which were generated by Shapiro reaction[11,12] on the 2,4,6-tri-ispopropylbenzenesulfonyl hydrazone of methyl vinyl ketone. The conjugate addition[13] produced in modest yield (68%) a mixture of isomers that was largely (ca. 95%) the cis compound **8**. When the crude material was treated with vinylmagnesium bromide, it was possible to isolate triene **9** (73%) as a single isomer. The stereochemistry at C-4 (ottelione numbering) was not established, as that center is subsequently converted to sp^2 hybridization. The triene underwent smooth ring closing metathesis[14] (78%) in the presence of 5 mol % Grubbs I catalyst at room temperature to afford the single alcohol **10**. Finally, Dess–Martin oxidation gave **5**[15]—the core of ottelione A.



5

In order to produce the isomeric trans-ring fused compound **3**, the adduct from the conjugate addition was isomerized by prolonged treatment (48 h) with DBU at room temperature (**8**→**11**). This experiment afforded a material that was highly enriched in the trans isomer **11** (ca. 85% trans), and reaction with vinylmagnesium bromide allowed isolation (67%) of a mixture of the trans alcohols **12**, epimeric at C-4. Without separation, these were treated with the Grubbs I catalyst (**12**→**13**), and the resulting alcohols,[16] were converted efficiently by Dess–Martin oxidation into **3**[17]—the core of ottelione B.

A cursory examination was made of the possibility of equilibrating the cis and trans isomers. The cis isomer appeared to be inert to the action of DBU in CH_2Cl_2 (room temperature, 48 h), or at reflux in DME (12 h) or PhMe (12 h). Conversely, the trans isomer **3** was converted to only a small extent (<10%), if at all, by warming with $TsOH{\cdot}H_2O$ in THF.[6] Deprotonation with LDA, and reprotonation appeared to give a 77:23 mixture in favor of the trans isomer. The selectivity among the double bonds in the two ring closing metathesis reactions is precedented[14] but, in the case of **12**, it was not clear what influence the trans disposition of the pendants might have; fortunately, the conversion to **13** does



Scheme 2.

not involve any seriously strained intermediate, and the yield is satisfactory.

The approach of Scheme 2 is very simple and, in principle, it should be applicable to other ottelione analogs, but we have not (yet) demonstrated this.

Acknowledgments

We thank the Natural Sciences and Engineering Research Council of Canada for financial support. D.L. holds a Province of Alberta Graduate Fellowship. We thank Dr. Stephen Fletcher for the isomerization studies with **5**.

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15. Compound **5** had: FTIR (CH_2Cl_2 cast) 2953, 2871, 1664, 906 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53–1.66 (m, 3H), 1.85–1.93 (m, 2H), 2.20–2.25 (m, 1H), 2.76 (dd, J = 7.8, 11.3 Hz, 1H), 3.06 (dd, J = 7.8, 16.3 Hz, 1H), 5.37 (d, J = 5.8 Hz, 2H), 5.92 (d, J = 5.8 Hz, 1H), 6.97 (d, J = 9.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8 (s), 145.5 (d), 143.4 (s), 126.6 (d), 120.4 (t), 49.2 (d), 44.4 (d), 33.6 (t), 27.7 (t), 23.0 (t); exact mass m/z calcd for $C_{10}H_{12}O$ 148.08882, found 148.08852.
16. The material was a mixture of α and β isomers in a 73:27 ratio, the α-alcohol being identified by spectral comparison with the sample described in Ref. 6.
17. Compound **3** had: ^1H NMR (500 MHz, $CDCl_3$) δ 1.66–1.71 (m, 1H), 1.75–1.82 (m, 3H), 1.93–1.98 (m, 1H), 2.03–2.07 (m, 1H), 2.38–2.43 (m, 1H), 2.53–2.58 (m, 1H), 5.24 (s, 1H), 5.33 (s, 1H), 5.96 (d, 1H, J = 9.6 Hz), 7.05 (d, 1H, J = 9.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3 (s), 147.1 (d), 145.5 (s), 128.8 (d), 116.4 (t), 54.1 (d), 47.6 (d), 27.6 (t), 23.3 (t), 21.6 (t).