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An expedient synthesis of (±)-centrolobine

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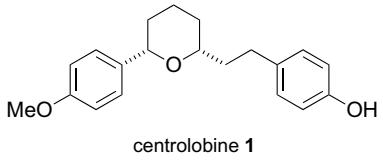
Abstract—An expedient synthesis of the antibiotic natural product centrolobine is reported, the key step being the one pot, multi-component construction of a tetrahydropyran-4-one via a 'revisited' Maitland–Japp reaction.

Centrolobine **1** (Fig. 1) is a 2,6-disubstituted tetrahydropyran with antibiotic properties, which was isolated from the heartwood of *Centrolobium robustum* and the stem of *Brosinium potabile* in the Amazon forest.[1]



centrolobine **1**

Figure 1.

To date there has been one total synthesis of the racemic methyl ether[1a,2] and four total syntheses of (−)-centrolobine.[3–6] All of these total syntheses have been reported over the last 2 years and centrolobine has become a testing ground to highlight new developments in the construction of tetrahydropyran rings. For example, the first total synthesis by Colobert et al.[3] featured the reduction of a β-ketosulfoxide followed by an intramolecular cyclization and yielded the natural product in nine steps. The second synthesis by Rychnovsky[4] utilized a Prins cyclization as the key step and furnished (−)-centrolobine in seven steps. A synthesis by Evans[5] at Indiana, formed the tetrahydropyran ring by an intramolecular reductive etherification strategy and provided the natural product in five steps from aldehyde **2**. Finally, Cossy reported a four step synthesis of (−)-centrolobine in an overall yield of 7%.[6] We saw an opportunity to apply our recent renaissance of the Maitland–Japp reaction[7] (Fig. 2) as a key step in the synthesis of (±)-centrolobine, and hence attempt to reduce the number of synthetic steps further and increase the overall yield of centrolobine.

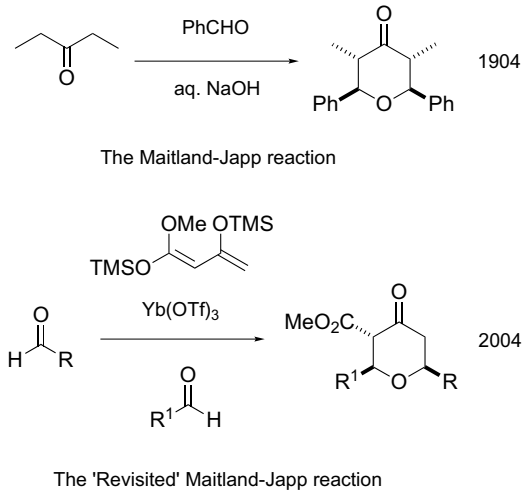


Figure 2.

Our synthesis of centrolobine (Scheme 1) utilized the same aldehyde as Evans as a starting point[5,8] which was subjected to our one pot, three-component 'revisited' Maitland–Japp reaction of Chan's diene **3**,[9] followed by the addition of anisaldehyde. This furnished tetrahydropyran-4-ones **4** and **5** in an excellent 92% yield and with an equilibrium ratio of 2:1.[10] The yield

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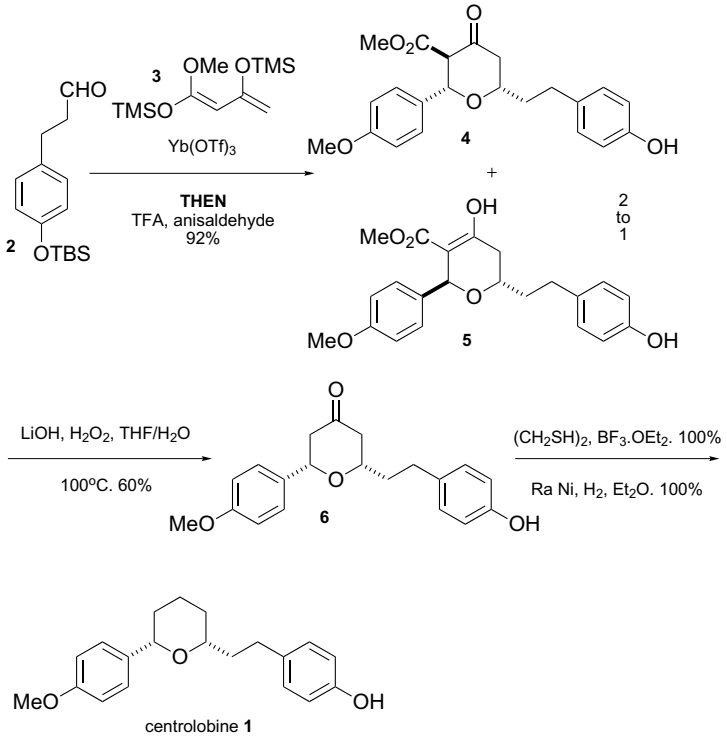

Scheme 1.

of the desired diastereomer **4** could be maximized by resubmission of **5** to the Lewis acidic reaction conditions. In this manner the undesired **5** was converted to a 2:1 ratio of **4**:**5** and, hence, the total yield of **4** increased from 60% to 82%. Decarboxylation of **4** using LiOH and H_2O_2 provided **6** in 60% yield. The remaining mass balance was material resulting from a retro-Michael reaction. These nonstandard decarboxylation conditions were used as it was discovered that if just LiOH was employed then the product of a retro-Michael reaction was formed exclusively, rather than that of decarboxylation. We rationalised that the less basic, more nucleophilic hydroperoxide anion favored saponification of the ester via nucleophilic attack at the carboxyl group rather than enolate formation, which led to elimination. Initially direct removal of the carbonyl group by Wolff–Kishner reduction was attempted. However, this was not possible as while formation of the hydrazone was facile, it was untouched by treatment with KOH. We believe this was due to deprotonation of the phenolic hydroxyl group under the reaction conditions. Removal of the carbonyl group was finally achieved by the formation of the dithiane followed by treatment with Raney nickel. This gave (±)-centrolobine in 100% yield over the two steps. A sample of our synthetic (±)-centrolobine was spectroscopically identical to the data reported for the previous four syntheses of (−)-centrolobine.

In summary, we have achieved an expedient total synthesis of (±)-centrolobine from aldehyde **2** in four steps and in an overall yield of 50%. This places our synthesis as the shortest and highest yielding synthesis of this molecule to date.

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References and notes

1. (a) De Albuquerque, I. L.; Galeffi, C.; Casinovi, C. B.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1964**, 287; (b) Alcantara, A. F.; de, C.; Souza, M. R.; Pilo-Weloso, D. *Fitoterapia* **2000**, *71*, 613.
2. Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1965**, 95.
3. Colobert, F.; Mazery, R. D.; Solladie, G.; Carreno, M. C. *Org. Lett.* **2002**, *4*, 1723, and; Carreno, M. C.; Mazery, R. D.; Urbano, A.; Colobert, F.; Solladie, G. *J. Org. Chem.* **2003**, *68*, 7779.
4. Marumoto, S.; Jaber, J. J.; Vale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919.
5. Evans, P. A.; Cui, J.; Gharpure, S. *J. Org. Lett.* **2003**, *5*, 3883.
6. Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadere, B. *Tetrahedron Lett.* **2004**, *45*, 6603.
7. (a) Japp, F. R.; Maitland, W. *J. Chem. Soc.* **1904**, *85*, 1473; (b) For preliminary studies see: Clarke, P. A.; Martin, W. H. C. *Org. Lett.* **2002**, *4*, 4527.
8. Jones, G. B.; Heaton, S. B. *Tetrahedron: Asymmetry* **1993**, *4*, 261.
9. Chan, T. H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534.
10. Experimental details for the 'revisited' Maitland–Japp reaction. Synthesis of **4**: Chan's diene **3** (260 mg, 1.00 mmol) was added to a solution of aldehyde **2** (132 mg, 0.50 mmol) and $Yb(OTf)_3$ (310 mg, 0.50 mmol) in CH_2Cl_2 (5.0 mL) at −78 °C. TFA (228 mg, 2.00 mmol)

was added after 150 min followed, after a further 5 min, by anisaldehyde (83 mg, 0.60 mmol). The solution was warmed to room temperature and stirred for a further 5 h. After this time the reaction mixture was diluted with Et_2O and washed successively with 10% aqueous $NaHCO_3$ solution and brine. The organics were dried ($MgSO_4$) and removed in vacuo. The residue was purified by flash column chromatography (10% EtOAc–Petrol) to yield **4** (115 mg, 60%) and **5** (62 mg, 32%). Data for **4**. ν_{max} (solution; $CHCl_3$) 3598, 2955, 2930, 1744, 1714, 1614, 1514, 1436, 1251, 1216, 1176, 1126 and 1035 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.32 (2H, d, $J = 8.4$ Hz), 7.00 (2H, d, $J = 8.4$ Hz), 6.89 (2H, d, $J = 8.0$ Hz), 6.74 (2H, d, $J = 8.4$ Hz), 5.37 (1H, s), 4.81 (1H, d, $J = 10.7$ Hz), 3.81 (3H, s), 3.81 (1H, dddd, $J = 11.2$, 7.6, 4.4, and 2.4 Hz), 3.60 (3H, s), 2.71 (2H, m), 2.56 (1H, dd, $J = 14.6$ and 2.4 Hz), 2.46 (1H, dd, $J = 14.6$ and 11.2 Hz), 2.03 (1H, m) and 1.85 (1H, m) ppm; δ_C (100 MHz; $CDCl_3$) 202.0, 168.0, 154.0, 133.0, 130.9, 129.4, 128.1, 114.0, 80.4, 76.0, 55.2, 30.2, 46.9, 37.8, and 30.9 ppm; MS (ES) *m/z* 384 (M^+) and 325 ($M^+ - CO_2Me$); found M^+ 384.1561, $C_{22}H_{24}O_6$ requires M^+ 384.1573.