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Asymmetric synthesis of the pyran antibiotic (−)-centrolobine☆

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Abstract—An expedient total synthesis of (−)-centrolobine is achieved involving asymmetric Keck allylation and stereoselective intramolecular oxy-Michael reactions as key steps in 8% overall yield.

2,6-Disubstituted tetrahydropyran scaffolds have gained prominence recently owing to their excellent biological properties.[1] This unit is also present in several natural products with cis stereoconnectivity at the 2,6-positions. Some recent examples, which fall into this class, include leucascandrolides,[2] phorboxazoles,[3] (+)-SCH 351448,[4] (−)-centrolobine and others. Owing to the challenges posed by the substitution pattern and also due to the interesting biological properties, the synthesis of these compounds has attracted attention. Various approaches leading to (−)-centrolobine have been reported (Fig. 1).[5]

Our own interest in the synthesis of enantiopure bioactives[6] prompted us to explore the possibility of synthesizing (−)-centrolobine, the results of which are presented herein. Retrosynthetic analysis of (−)-centrolobine revealed two fragments **2** and **3**. 4-Tosyloxybenzaldehyde was subjected to Keck allylation[7] with allyltributyltin in the presence of (*S*)-BINOL and $Ti(O^iPr)_4$ to produce homoallylic alcohol **4** in 73% yield. The optical purity of **4** was found to be 97% ee by chiral HPLC. Protection of the 2° hydroxyl group as the TBS ether followed by detosylation and methylation furnished **5** in 53% overall yield (Scheme 1).

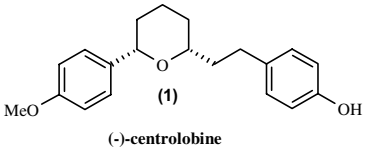
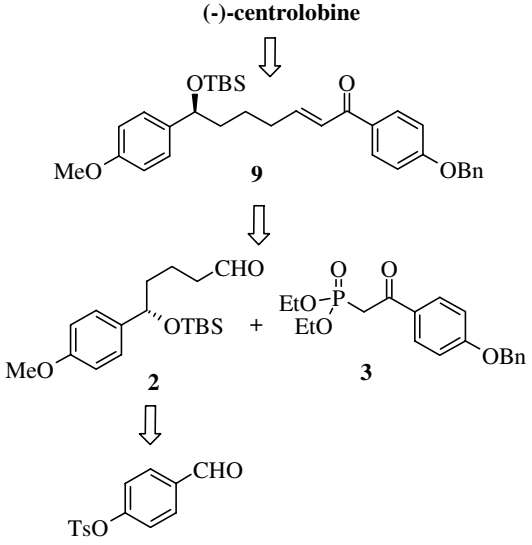


Figure 1.

Hydroxyl protecting group manipulation was necessary as allylation of 4-methoxybenzaldehyde under Keck conditions was not successful in our hands, whilst Ipc_2B-(allyl)[8] gave a high yield of the allylated product (89%), but with poor enantioselectivity. One-pot ozonolysis-Wittig olefination[9] was quite effective to give the α,β-unsaturated ester **6** in 84% yield. One-pot reduction of the olefin and ester groups with excess $LiAlH_4$ furnished **8** in synthetically unacceptable yields but this could be circumvented by stepwise olefin reduction with Mg/MeOH[10] to furnish **7** in 81% yield followed by ester



Scheme 1. Retrosynthetic analysis.

Keywords: Keck allylation; Intramolecular oxy-Michael reaction; (−)-Centrolobine; 2,6-Disubstituted tetrahydropyran.
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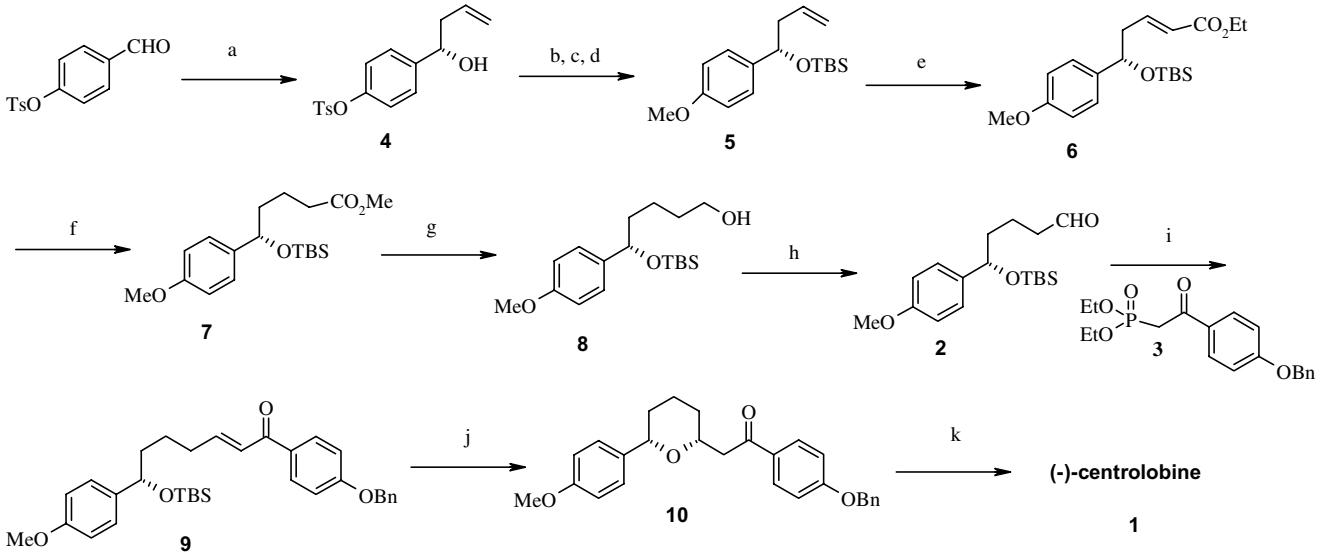

Scheme 2. Reagents and conditions: (a) (*S*)-BINOL, $Ti(^iOPr)_4$, allyltributyltin, 4 Å MS, CH_2Cl_2, −20 °C, 70 h, 73%, 97% ee; (b) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 4 h, 87%; (c) Mg/MeOH, rt, 3 h, 85%; (d) K_2CO_3, MeI, acetone, 0 °C to reflux, 4 h, 73%; (e) (i) O_3, CH_2Cl_2, −78 °C, 1 h, then TPP; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 2 h, 84% (for two steps); (f) Mg/MeOH, rt, 3 h, 81%; (g) LAH, THF, 0 °C to rt, 3 h, 76%; (h) IBX, DMSO, rt, 4 h, 80%; (i) **3**, $Ba(OH)_2{\cdot}8H_2O$, THF/H_2O (4:1), rt, 5 h, 81%; (j) HF–Py, THF, 0 °C to reflux, 4 h, 80%; (k) Pd/C, H_2 atm, HCl, EtOH/EtOAc/H_2O (5:1:1), 10 h, 70%.

reduction at 0 °C with LAH yielding **8** in 76% yield. To install the requisite enone for intramolecular oxy-Michael reaction, the 1° alcohol group in **8** was oxidized[11] with IBX to 5-aryl pentanaldehyde derivative **2** in 80% yield, which on further homologation with Horner's phosphonate[12] **3** under mild basic conditions provided the key synthon **9** in 81% yield. The olefin geometry could not be assigned from the ^1H NMR spectrum as the resonances corresponding to the olefin overlapped with the aromatic protons. However, the ^{13}C spectrum was homogeneous (δ 130.7 and 114.8). Exposure of silyl ether-enone **9** to HF-pyridine triggered in situ silyl cleavage followed by intramolecular oxy-anion Michael addition[13] to provide substituted pyran **10** in 4 h and in 80% yield. The '*syn*' selectivity of the 2,6-disubstituted pyran was confirmed by cleavage of the benzyl ether with Pd/C/HCl[14] to furnish (−)-centrolobine. In the absence of HCl the pyran ring was destroyed.[15] The optical purity and other spectral data[16] were in full accordance with those reported for the natural product (Scheme 2).

In summary, we have achieved the stereoselective total synthesis of (−)-centrolobine. This general strategy for synthesizing the *cis*-pyran skeleton should allow the preparation of structurally related compounds.

Acknowledgements

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References and notes

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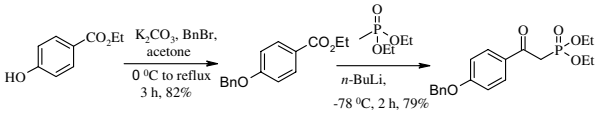
12. Solladie, G.; Wilb, N.; Bauder, C. *J. Org. Chem.* **1999**, *64*, 5447–5452. The Horner phosphonate was synthesized from commercially available ethyl *para*-hydroxybenzoate. (i) Protection of the phenol as the benzyl ether. (ii) The ester was treated with methyl diethylphosphonate.



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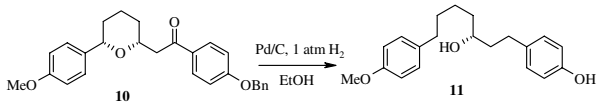
15. Compound **10** was subjected to standard catalytic hydrogenation (Pd/C, 1 atm of H_2, EtOH) to yield the ring cleaved compound **11** as the sole product (Ref. 5f).



16. Spectral data for selected compounds:
Compound **9**: $[\alpha]_D^{25}$ −41.7 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, $J = 8.8$ Hz, 2H), 7.59–7.45 (m, 5H), 7.32 (d, $J = 8.5$ Hz, 2H), 7.21–7.05 (m, 3H), 7.03–6.88 (m, 3H), 5.27 (s, 2H), 4.75 (t, $J = 6.7$ Hz, 1H), 3.93 (s, 3H), 2.60–2.27 (m, 2H), 1.98–1.57 (m, 4H), 1.01 (s, 9H), 0.15 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.4, 189.4, 162.6, 158.8, 148.8, 137.2, 130.7, 128.6, 128.2, 127.4, 126.9, 125.5, 114.5, 113.4, 74.7, 70.2, 55.15, 44.0, 40.2, 32.8, 25.8, 24.4, 18.2, −4.6, −4.9; MS (LC): *m/z* 531 (M^++H); IR (neat) cm^{-1} 2942, 1726, 1609, 1510, 1461, 1248, 1172, 1087, 835.
Compound **10**: $[\alpha]_D^{25}$ −54.40 (*c* 0.5, $CHCl_3$); solid, mp 132–135 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, $J = 8.8$ Hz, 2H), 7.46–7.29 (m, 5H), 7.16 (d, $J = 8.6$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 6.76 (d, $J = 8.6$ Hz, 2H), 5.11 (s, 2H), 4.35 (d, $J = 8.6$ Hz, 1H), 4.20–3.99 (m, 1H), 3.77 (s, 3H), 3.32 (dd, $J = 6.7$, 15.7 Hz, 1H), 2.97 (dd, $J = 6.7$, 15.7 Hz, 1H), 2.04–1.57 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 162.5, 158.7, 136.2, 135.4, 130.7, 130.5, 128.6, 128.1, 127.3, 127.0, 114.4, 113.5, 79.4, 75.1, 70.0, 55.2, 45.2, 33.0, 31.6, 23.8; MS (LC): *m/z* 417 (M^++H), 211; IR (neat) cm^{-1} 3443, 2930, 1608, 1359, 1248, 1096, 794.
Compound **11**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.03–6.89 (m, 4H), 6.75–6.61 (m, 4H), 3.76 (s, 3H), 3.60–3.47 (m, 1H), 2.65–2.47 (m, 4H), 1.72–1.18 (m, 8H); MS (LC); *m/z* 315 (M^++H).
Compound **1**: solid, mp 82–85 °C; $[\alpha]_D^{25}$ −91.7 (*c* 0.5, $CHCl_3$), lit.[1c,5b]; mp 84–86 °C, $[\alpha]_D^{25}$ −93.1 (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, acetone-d_6): δ 8.06 (s, OH), 7.31 (d, $J = 8.6$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 6.74 (d, $J = 8.4$ Hz, 2H), 4.30 (dd, $J =$ 1.9, 11.2 Hz, 1H), 3.78 (s, 3H), 3.46–3.41 (m, 1H), 2.71–2.57 (m, 2H), 1.91–1.62 (m, 6H), 1.46–1.37 (m, 1H), 1.33–1.24 (m, 1H); ^{13}C NMR (50 MHz, acetone-d_6) δ 160.4, 157.0, 137.9, 134.7, 130.9, 128.5, 116.7, 115.0, 80.6, 78.4, 56.2, 40.3, 35.4, 32.9, 32.2, 25.5; MS (LC): *m/z* 313.1 (M^++H), 107; IR (neat) cm^{-1} 3401, 2934, 1613, 1513, 1247, 1034.