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A TOTAL ASYMMETRIC SYNTHESIS OF (+)-ar-TURMERONE

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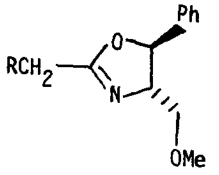
Summary: Employing a chiral oxazoline, a total synthesis of the title compound is described.

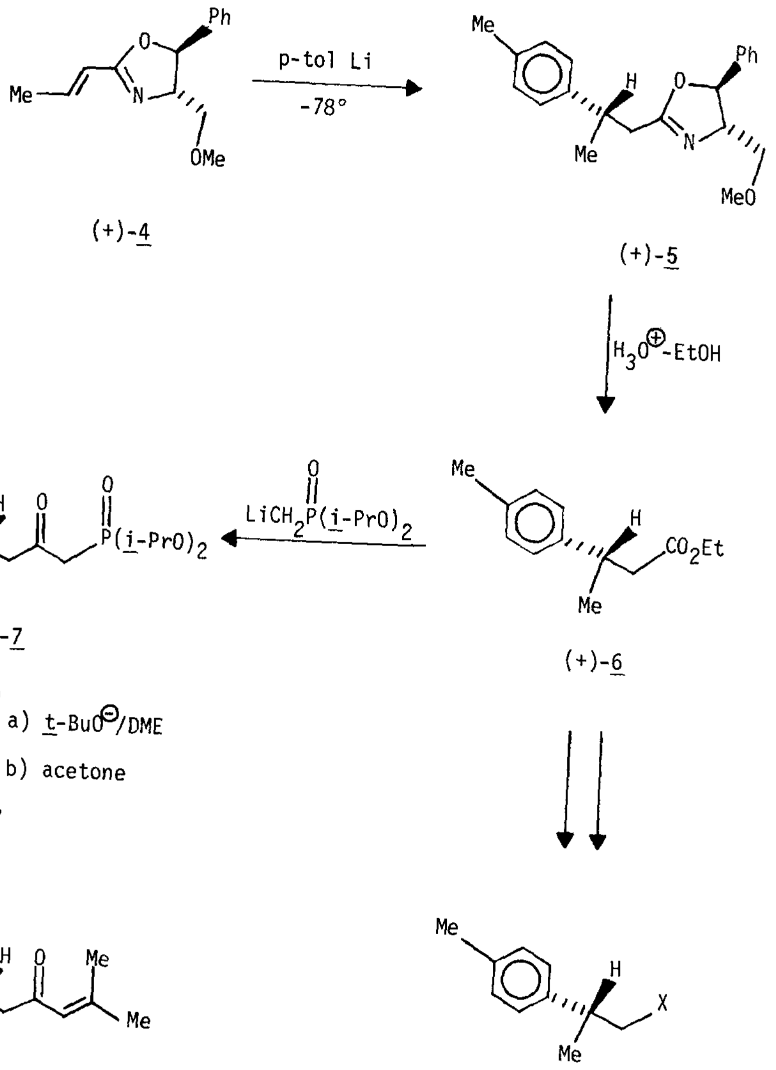
The monocyclic aromatic sesquiterpene (+)-ar-turmerone, 1, the chief component of the essential oil from rhizomes of Curcuma Longa Linn has been the subject of many studies.[1-3] A number of syntheses have been reported[4-8] leading to racemic 1, but none are able to provide natural material. We now describe a short, efficient asymmetric total synthesis of (+)-1 based upon methodology developed in our laboratory which furnishes β-substituted valerolactones in essentially 100% enantiomeric excess.[9]

The synthetic scheme is initiated by the chiral oxazoline 2 which is transformed into the phosphonate 3 [LDA, $(\underline{i}\text{-PrO})_2POCl$] and then condensed with acetaldehyde-potassium t-butoxide to furnish exclusively the E-propenyloxazoline, 4 [81%, $[\alpha]_D$ +38.0° ($CHCl_3$)] as previously described.[9c] The key asymmetric induction step was carried out by slow (1.5 h) addition of 4 to a THF solution of 1.4 equiv of p-tolyllithium (-78°, argon). After quenching with 1.4 equiv of acetic acid (-78° to ambient), the reaction worked up to yield, after preparative layer chromatography (Silica gel ethyl acetate-chloroform, 1:1) (+)-5 in 33% yield. The modest yield is due, not to diastereomeric separation,[10] but to competing proton abstraction on the methyl group in 4. Examination of 5 using hplc (Waters) indicated a 98.8% diastereomeric preference of diastereomers[11] consistent with other examples observed in this unique reaction.[9] Hydrolysis (ethanol-3M sulfuric, 1:1, reflux 6 h) gave the known[3] chiral ester 6 [79%, $[\alpha]_D$ +25.4° (2.17, $CHCl_3$), reported $[\alpha]_D$ +25.0°] in essentially 100% enantiomeric excess which confirmed the degree of asymmetric induction in the previous step, 4 to 5. Treatment of (+)-6 with 2.0 equiv of lithio methyldiisopropylphosphonate (n-BuLi, $CH_3PO(\underline{i}\text{-PrO})_2$, -78°) gave the β-ketophosphonate (+)-7 in 75% yield[12] as a useful precursor to the target product. The latter, when treated with 1.0 equiv of potassium tert-butoxide in dimethoxyethane (25°, 30 min) followed by addition of anhydrous acetone, gave (+)-ar-turmerone 1 in 71% yield virtually



(-)-2, R=H

(-)-3, R = $(\underline{i}\text{-PrO})_2\overset{\overset{O}{\|}}{P}$



(+)-4

(+)-5

(+)-6

(+)-7

(+)-1

8, X = CH_2I

9, X = CHO

identical in all respects with the literature data[13] $[[\alpha]_D^{22}$ +64° (c 4.5 hexane), Lit.[3] $[\alpha]_D$ 68° (neat)].

This route is applicable (via the ester 6) to other members of the bisabolane family by conversion to the chiral iodide 8 and aldehyde 9. In this fashion routes are now open to natural curcumene[14] nuciferal,[15] and E-nuciferal.[16]

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10. The various bands on the plc plate were examined (nmr) for inadvertent diastereomeric separations, however, only starting material, dimeric, and polymeric substances were noted.
11. Physical data for (+)-5: $[\alpha]_D^{22}$ +11.9°, $[\alpha]_{578}$ +12.6°, $[\alpha]_{546}^{22}$ +14.8°, $[\alpha]_{436}$ +31.1° (c 4.7, $CHCl_3$); nmr (CCl_4) δ 7.1 (m, 9), 5.1 (d, J=6 Hz, 1), 4.0-2.9 (m, 4), 3.3 (s, 3), 2.5 (d, J=8 Hz, 2), 2.3 (s, 3), 1.3 (d, J=7 Hz, 3); ir (neat film), 1665 cm^{-1}; tlc (silica gel, 17% acetone-hexane, R_f 0.27.
12. Physical data for (+)-7: $[\alpha]_D^{22}$ +18.7°, $[\alpha]_{578}$ +19.8°, $[\alpha]_{546}$ +23.5°, $[\alpha]_{436}$ +52.8° (c 3.07, $CHCl_3$); n_D^{23} 1.4852; nmr (CCl_4) δ 7.0 (s, 4), 4.6 (hept, J=5 Hz, 2), 3.2 (hex, J=6 Hz, 1), 2.9 (d, J=5 Hz, 2), 2.8 (d, J=23 Hz, 2), 2.3 (s, 3), 1.5-1.2 (m, 12); ir (neat film), 1715, 1250, 1000 cm^{-1}. Anal. %C (calcd.) 63.51; (found) 63.30; %H (calcd.) 8.59; (found 8.75. The analytical sample was obtained by bulb-to-bulb distillation; 125-135° (0.4 torr).

13. Purified by plc (silica gel, CH_2Cl_2) R_f 0.78, nmr (CCl_4); 7.0 (s, 4), 5.9 (s, 1), 3.2 (hex, J=7 Hz, 1), 2.5 (d, J=7 Hz, 2), 2.2 (s, 3), 2.0 (s, 3), 1.8 (s, 3), 1.2 (d, J=6 Hz, 3); ir (neat film) 1690, 1620 cm^{-1}; $[\alpha]_D^{22}$ +64 $[\alpha]_{578}$ +67.4°, $[\alpha]_{546}$ +79.1°, $[\alpha]_{436}$ +169.4° (c 4.5, hexane).
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