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## Synthesis of (+/-)-Curcumene Ether

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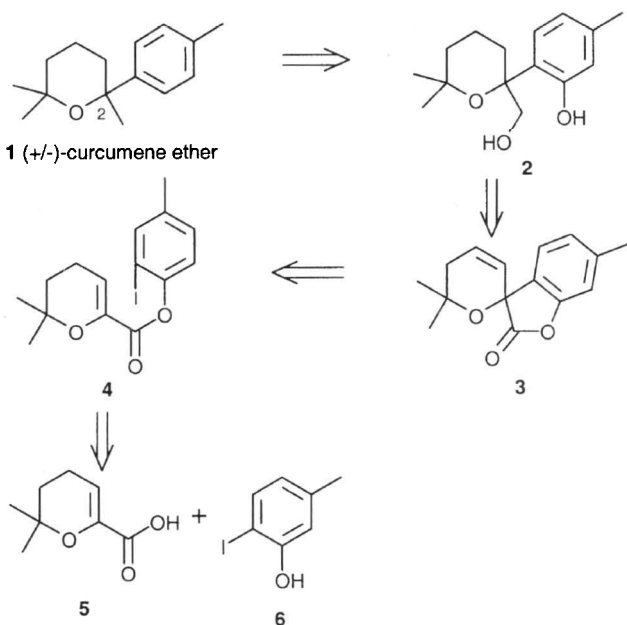
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**Abstract:** A 9 step synthesis of (+/-)-curcumene ether is described starting from 5-bromo-2-methyl-2-pentene and 2-amino-5-methylphenol in 7% overall yield using an intramolecular Heck reaction as the key transformation to generate a stereogenic quaternary center.

**Key words:** total synthesis, intramolecular Heck reaction, spiro compounds, lactones, natural products

Our interest in the asymmetric intramolecular Heck reaction as a key step for the synthesis of natural products<sup>1</sup> has resulted in our expanding the application of this reaction towards the synthesis of pyran containing natural products<sup>2</sup> whereby a stereogenic center is created at the C-2 position of the pyran ring. To our knowledge, the intramolecular Heck strategy<sup>3</sup> has not been used to generate pyran rings containing an aryl group as one of the substituents on the stereogenic center at C-2. This paper describes the synthesis of (+/-)-curcumene ether (**1**) in which the stereogenic center is created via an intramolecular Heck reaction.



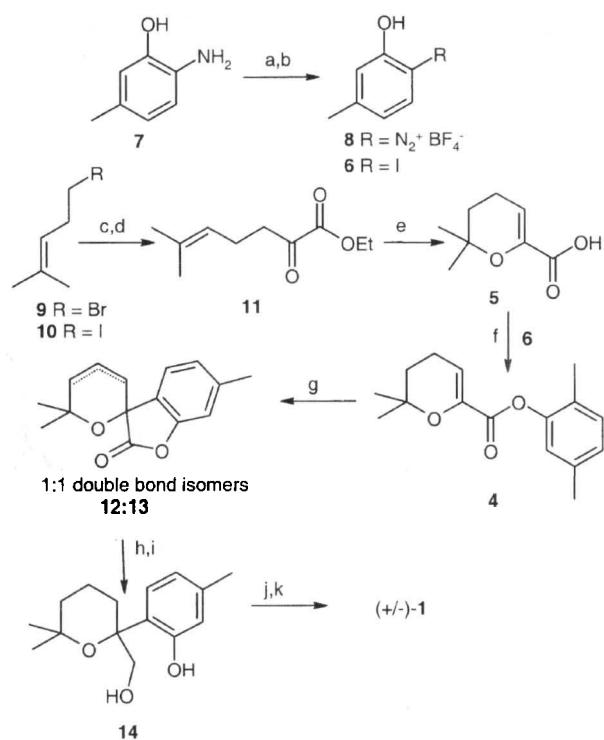
Scheme 1

The sesquiterpene curcumene ether (**1**) was isolated from the plant *Thuja orientalis* in 1969.<sup>4</sup> To date there have been three syntheses of (+/-)-**1** reported in the literature. The first of these was reported by Vig and coworkers<sup>5</sup> in 1973 but their synthesis could not be repeated by Paknikar and coworkers in 1980.<sup>6</sup> Consequently, there are only two valid syntheses of (+/-)-**1**. The first by Mashrequi and Trivedi<sup>7</sup> in 1978 and the second by Kametani et al in 1984.<sup>8</sup> Only recently has the first stereoselective synthesis of (*R*)-(+)-**1** been reported by Serra.<sup>9</sup> This synthesis involved a resolution of cinenic acid and provided (*R*)-(+)-**1** in 13 steps with an overall yield of 3%.

The retrosynthesis towards curcumene ether (**1**) is illustrated in Scheme 1. Retrooxygenation of **1** at the C-2 methyl group and *ortho*-position of the aromatic ring provides **2**. Retrooxidation of the hydroxymethyl group and ring closure to a lactone gives **3** that should be formed via an intramolecular Heck reaction with ester **4**. Disconnection of ester **4** gives acid **5** and iodophenol **6**. Compounds **5** and **6** are easily prepared as outlined in Scheme 2.

2-Iodo-5-methylphenol (**6**) was prepared by diazotization of 2-amino-5-methylphenol (**7**)<sup>10</sup> with isoamyl nitrite and HBF<sub>4</sub> in ether to give the stable diazonium tetrafluoroborate intermediate **8** in 86% yield.<sup>11</sup> Treatment of **8** with NaI in refluxing acetone afforded the 2-iodo-5-methylphenol (**6**)<sup>12</sup> in 71% yield.

The synthesis of pyran acid **5** started with 5-bromo-2-methyl-2-pentene (**9**).<sup>13</sup> Bromide **9** was converted to iodide **10** using NaI in acetone. Halogen-metal exchange of iodide **10** with *t*-BuLi (ether, -78 °C) provided an alkyllithium species that was added slowly to a -78 °C solution of 10 equiv of diethyl oxalate in ether. Standard workup provided ketoester **11** in 52% yield from bromide **9**. Hydrolysis of ester **11** to an acid followed by purification by distillation unexpectedly gave pyran acid **5** in 65% yield. Previous syntheses of **5** from the corresponding acid of **11**<sup>13</sup> required heating the acid with formic acid for 15 minutes. In our hands, the heat applied during the distillation must result in the acid auto catalyzing itself to form pyran **5** in the distillation bulb. DCC coupling of acid **5** and phenol **6** in CH<sub>2</sub>Cl<sub>2</sub> with DMAP gave **4** in 88% yield. With ester **4** in hand, the intramolecular Heck cyclization was attempted. Treatment of a mixture of pentamethylpiperidine and **4** in *N,N*-dimethylacetamide (DMA) with a mixture of Pd<sub>2</sub>(dba)<sub>3</sub> and (+/-)-BINAP (in DMA) followed by refluxing the solution for 4 d provided a 1:1 mixture of double bond isomers **12** and **13**.<sup>14-16</sup> Changing the source of Pd, base and/or solvent resulted in complex



**Scheme 2** Reagents and conditions: a)  $\text{HBF}_4$ ,  $\text{Et}_2\text{O}$ , isoamyl nitrite,  $\text{EtOH}$ ,  $0^\circ\text{C}$ , 30 min (86%); b)  $\text{NaI}$ , acetone, reflux, 3 d (71%); c)  $\text{NaI}$ , acetone, r.t., 20 h (92%); d) 2 equiv. *t*-BuLi,  $\text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$ , 1 h; then 10 equiv diethyl oxalate,  $\text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$ , 4 h (52% 2 steps); e)  $\text{KOH}$ ,  $\text{H}_2\text{O}$ ,  $\text{EtOH}$ , reflux, 20 h; 1%  $\text{HCl}$ , purification at  $100^\circ\text{C}$ , 0.4 mmHg (64%); f) **6**, DCC, DMAP,  $\text{CH}_2\text{Cl}_2$ , r.t., 20 h (88%); g)  $\text{Pd}_2(\text{dba})_3$ , (+/-)-BINAP, *N,N*-dimethylacetamide,  $\text{N}_2$ , r.t., 45 min; then add to **4**, pentamethylpiperidine, *N,N*-dimethylacetamide, argon,  $100^\circ\text{C}$ , 4 d (90%); h)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ , r.t., 20 h; i) 1 atm  $\text{H}_2$ , 5%  $\text{Pd/C}$ ,  $\text{EtOH}$ , r.t., 20 h (86%, 2 steps); j) 2.2 equiv  $\text{NaH}$ , THF, then add diethylchlorophosphate, r.t., 2 h; k)  $\text{Li}_{(s)}$ ,  $\text{NH}_{30}$ ,  $\text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$ , 30 min (57%, 2 steps).

mixtures wherein unreacted SM, **12**, **13** and deiodized **4** were obtained in varying ratios. Changing the time and temperature of the reaction did not noticeably change the ratio of **12:13**. This was not a worry as the double bond was not necessary for the synthesis of curcumene ether. Reduction of the mixture of lactones **12** and **13** with  $\text{LiAlH}_4$  followed by a catalytic hydrogenation of a mixture of the isomeric olefins gave saturated diol **14** in 86% yield. The last step of the synthesis involved removal of both the hydroxyl and phenol groups simultaneously. This was accomplished by converting diol **14** into a bis(diethylphosphonate)<sup>17</sup> followed by removal of both phosphonates by treatment with lithium metal in liquid ammonia to give (+/-)-curcumene ether (**1**) in 57% yield from **14**.

In conclusion, we have developed a 9-step synthesis of (+/-)-curcumene ether (**1**) from 5-bromo-2-methyl-2-pentene (**9**) and 2-amino-5-methylphenol (**7**) in an overall yield of 7%. We are currently preparing 2-trifluoromethanesulfonyloxy-5-methylphenol in order to attempt the intramolecular Heck reaction under asymmetric conditions.<sup>15</sup> Applications of this strategy towards the synthesis of other 2-arylpyrans are currently underway.

## Acknowledgment

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- (15) Experimental procedure for the conversion of **4** to **12** and **13**: A mixture of  $\text{Pd}_2(\text{dba})_3$  (13 mg, 0.0141 mmol), (+/-)-BINAP (17.0 mg, 0.0273 mmol), and dry DMA (2.5 mL) under  $\text{N}_2$  was added after 45 min. via syringe to a 2 dram screw-top vial containing ester **4** (52.3 mg, 0.141 mmol). PMP (127  $\mu\text{L}$ , 0.705 mmol) was added and the mixture was heated in the sealed vial at  $100^\circ\text{C}$  for 4 days. The solution was poured into ether and washed with saturated  $\text{NaHCO}_3$  aq ( $4 \times 10$  mL) and  $\text{NaCl}$  aq ( $4 \times 10$  mL). The ether extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered and ether removed under reduced pressure to give a red/black residue. The oil was purified by flash chromatography (20:1, hexanes:  $\text{EtOAc}$ ) to give a mixture 1:1 mixture of **12** and **13** (31 mg, 90%). IR ( $\text{cm}^{-1}$ ) 1814 (ester C=O), 1629 (alkene C=C);  $^1\text{H NMR}$   $\delta$  1.35 (br s, 3 H, H-1 or H-2), 1.39 (br s, 3 H, H-10 or H-11), 1.43 (br s, 3 H, H-1 or H-2), 1.49 (br s, 3 H, H-10 or H-11), 2.31 (m, 2 H, H-14), 2.38 (br s, 6 H, H-8 and H-17), 2.44 (m, 2 H, H-3), 5.63 (dt, 1 H,  $J = 10.1$  Hz,  $J = 2.05$  Hz, H-12), 5.89–6.08 (m, 2 H, H-4 and H-5), 6.23 (dt, 1 H,  $J = 10.3$  Hz,  $J = 4.2$  Hz, H-13), 6.87–7.36 (m, 6 H, H-6, H-7, H-9, H-15,

H-16, and H-18);  $^{13}\text{C}$  NMR  $\delta$  21.8 ( $2 \times \text{CH}_3$ ), 28.6 ( $\text{CH}_3$ ), 29.0 ( $\text{CH}_3$ ), 29.9 ( $\text{CH}_3$ ), 30.1 ( $\text{CH}_3$ ), 30.8 ( $\text{CH}_2$ ), 35.8 ( $\text{CH}_2$ ), 72.9 ( $\text{C}_q$ ), 73.7 ( $\text{C}_q$ ), 74.9 ( $\text{C}_q$ ), 76.9 ( $\text{C}_q$ ), 111.6 ( $\text{CH}$ ), 111.7 ( $\text{CH}$ ), 118.3 ( $\text{CH}$ ), 124.0 ( $\text{CH}$ ), 124.4 ( $\text{CH}$ ), 124.7 ( $\text{CH}$ ), 125.0 ( $\text{CH}$ ), 125.3 ( $\text{CH}$ ), 126.6 ( $\text{C}_q$ ), 127.0 ( $\text{C}_q$ ), 127.4 ( $\text{CH}$ ), 135.6 ( $\text{CH}$ ), 141.1 ( $\text{C}_q$ ), 141.2 ( $\text{C}_q$ ), 153.1 ( $\text{C}_q$ ), 153.4 ( $\text{C}_q$ ), 174.8 ( $\text{C}_q$ ), 175.5 ( $\text{C}_q$ ); Mass spectra: (Compound **12**) 244 (1,  $\text{M}^+$ ), 216 (26,  $\text{M}^+ - \text{CO}$ ), 202 (14), 201 (100,  $\text{M}^+ - \text{CO}$  and  $-\text{CH}_3$ ), 187 (4), 135 (29), 134 (11), 67 (12); (Compound **13**) 244 (20,  $\text{M}^+$ ), 216 (22,  $\text{M}^+ - \text{CO}$ ), 202 (13), 201 (100,  $\text{M}^+ - \text{CO}$  and  $-\text{CH}_3$ ), 161 (50), 135 (40), 115 (14), 77 (14); Mass calculated for  $\text{C}_{15}\text{H}_{16}\text{O}_3$  ( $\text{M}^+$ ): 244.10994, found: 244.10954.

- (16) Attempts to perform the intramolecular Heck reaction on iodide **4** with enantiopure BINAP, BINAPFu,<sup>18</sup> TetFuBINAP<sup>19</sup> or Pfaltz's phosphinooxazoline ligand<sup>20</sup> gave racemic mixtures of double bond isomers **12** and **13**.
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