Synthesis of (+/−)-Curcumene Ether

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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[1] has resulted in our expanding the application of this reaction towards the synthesis of pyran containing natural products[2] whereby a stereogenic center is created at the C-2 position of the pyran ring. To our knowledge, the intramolecular Heck strategy[3] 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.
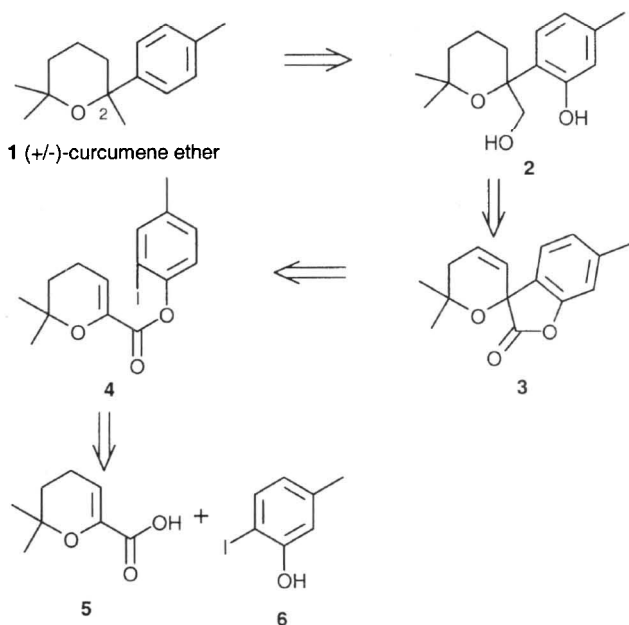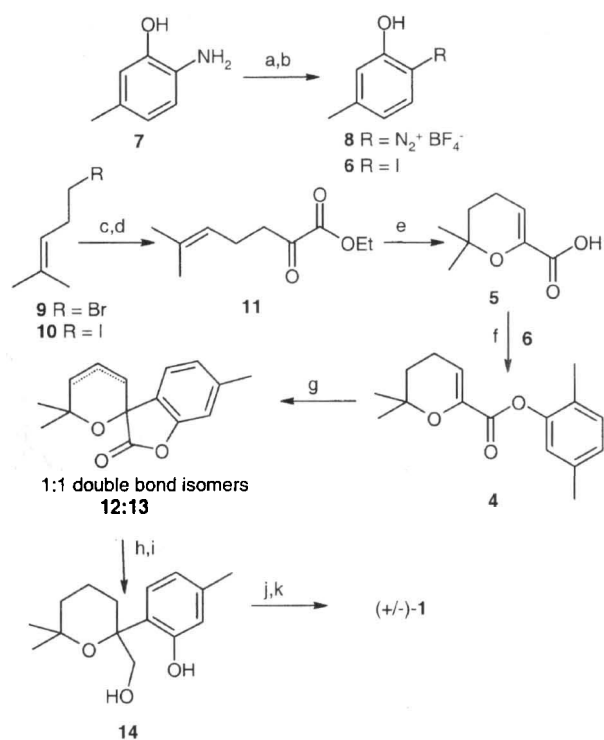

Scheme 1

The sesquiterpene curcumene ether (1) was isolated from the plant *Thuja orientalis* in 1969.[4] To date there have been three syntheses of (+/−)-1 reported in the literature. The first of these was reported by Vig and coworkers[5] in 1973 but their synthesis could not be repeated by Paknikar and coworkers in 1980.[6] Consequently, there are only two valid syntheses of (+/−)-1. The first by Mashrequi and Trivedi[7] in 1978 and the second by Kametani et al in 1984.[8] Only recently has the first stereoselective synthesis of (R)-(+)-1 been reported by Serra.[9] 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)[10] with isoamyl nitrite and HBF$_4$ in ether to give the stable diazonium tetrafluoroborate intermediate 8 in 86% yield.[11] Treatment of 8 with NaI in refluxing acetone afforded the 2-iodo-5-methylphenol (6)[12] in 71% yield.

The synthesis of pyran acid 5 started with 5-bromo-2-methyl-2-pentene (9).[13] 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[13] required heating the acid with formic acid for 15 minutes. In our hands, the heat applied during the distillation must resulted in the acid auto catalyzing itself to form pyran 5 in the distillation bulb. DCC coupling of acid 5 and phenol 6 in CH$_2$Cl$_2$ 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$_2$(dba)$_3$ and (+/−)-BINAP (in DMA) followed by refluxing the solution for 4 d provided a 1:1 mixture of double bond isomers 12 and 13.[14–16] Changing the source of Pd, base and/or solvent resulted in complex

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

mixtures wherein unreacted SM, **12**, **13** and deiodizied **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 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)[17] 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.[15] Applications of this strategy towards the synthesis of other 2-arylpyrans are currently underway.

References

(1) (a) Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766. (b) Lau, S. Y. W.; Keay, B. A. *Org. Lett.* **2001**, *3*, 181. (c) Lau, S. Y. W.; Keay, B. A. *Synlett* **1999**, 605. (d) Keay, B. A.; Maddaford, S. P.; Cristofoli, W. A.; Andersen, N. G.; Passafaro, M. S.; Wilson, N. S.; Nieman, J. A. *Can. J. Chem.* **1996**, *75*, 1163. (e) Cristofoli, W. A.; Keay, B. A. *Synlett* **1994**, 625.

(2) Woo, S.; Keay, B. A. *Synlett* **1996**, 135.

(3) (a) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (b) Ikeda, M.; ElBialy, S. A. A.; Yakura, T. *Heterocycles* **1999**, *51*, 1957. (c) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH, Inc.: New York NY, **1998**, 231. (d) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (e) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447.

(4) (a) Tomida, B.; Hirose, Y.; Nakatsuka, T. *Mokuzai Gakkaishi* **1969**, *15*, 47. (b) Tomida, B.; Hirose, Y. *Mokuzai Gakkaishi* **1969**, *15*, 337.

(5) Vig, O. P.; Kumar, H.; Salota, J. P.; Sharma, S. D. *Indian J. Chem.* **1973**, *11*, 86.

(6) Paknikar, S. K.; Dinge, A. S. *Indian J. Chem.* **1980**, *19*, 80.

(7) Mashrequi, S. H.; Trivedi, G. K. *Indian J. Chem.* **1978**, *16*, 849.

(8) Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1305.

(9) Serra, S. *Synlett* **2000**, 890.

(10) Purchased from the Aldrich Chemical Company.

(11) (a) Sawaguchi, M.; Fukuhara, T.; Yoneda, N. *J. Fluor. Chem.* **1999**, *97*, 127. (b) Yoneda, N.; Fukuhara, T.; Mizokami, T.; Suzuki, A. *Chem. Lett.* **1991**, 459.

(12) Cambie, R. C.; Rutledge, P. S.; Smith-Palmer, T.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1161.

(13) Hiranuma, S.; Shibata, M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 5321.

(14) (a) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.

(15) Experimental procedure for the conversion of **4** to **12** and **13**: A mixture of Pd$_2$(dba)$_3$ (13 mg, 0.0141 mmol), (+/–)-BINAP (17.0 mg, 0.0273 mmol), and dry DMA (2.5 mL) under 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 μL, 0.705 mmol) was added and the mixture was heated in the sealed vial at 100 °C for 4 days. The solution was poured into ether and washed with saturated NaHCO$_3$ aq (4 × 10 mL) and NaCl aq (4 × 10 mL). The ether extracts were dried over anhydrous 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: EtOAc) to give a mixture 1:1 mixture of **12** and **13** (31 mg, 90%). IR (cm^{-1}) 1814 (ester C=O), 1629 (alkene C=C); ^{1}H NMR δ 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}C NMR δ 21.8 (2 × CH$_3$), 28.6 (CH$_3$), 29.0 (CH$_3$) 29.9 (CH$_3$), 30.1 (CH$_3$), 30.8 (CH$_2$), 35.8 (CH$_2$), 72.9 (C$_q$), 73.7 (C$_q$), 74.9 (C$_q$), 76.9 (C$_q$), 111.6 (CH), 111.7 (CH), 118.3 (CH), 124.0 (CH), 124.4 (CH), 124.7 (CH), 125.0 (CH), 125.3 (CH), 126.6 (C$_q$), 127.0 (C$_q$), 127.4 (CH), 135.6 (CH), 141.1 (C$_q$), 141.2 (C$_q$) 153.1 (C$_q$), 153.4 (C$_q$), 174.8 (C$_q$), 175.5 (C$_q$); Mass spectra: (Compound **12**) 244 (1, M$^+$), 216 (26, M$^+$-CO), 202 (14), 201 (100, M$^+$-CO and -CH$_3$), 187 (4), 135 (29), 134 (11), 67 (12); (Compound **13**) 244 (20, M$^+$), 216 (22, M$^+$-CO), 202(13), 201 (100, M$^+$-CO and -CH$_3$), 161 (50), 135 (40), 115 (14), 77 (14); Mass calculated for C$_{15}$H$_{16}$O$_3$ (M$^+$): 244.10994, found: 244.10954.

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

(17) (a) Fuganti, C.; Serra, S. *J. Org. Chem.* **1999**, *64*, 8728.
(b) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1973**, *38*, 2314.

(18) Andersen, N. G.; Parvez, M.; Keay, B. A. *Org. Lett.* **2000**, *2*, 2817.

(19) Andersen, N. G.; McDonald, R.; Keay, B. A. *Tetrahedron: Asymmetry* **2001**, *12*, 263.

(20) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338.