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A Novel, Stereospecific Total Synthesis of (±)-$\Delta^{9(12)}$-Capnellene from p-Cresol

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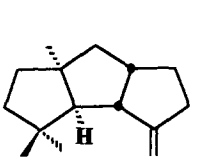
Abstract: A novel, efficient and stereospecific synthesis of (±) capnellene from p-cresol is reported.

There has been a world wide interest in the chemistry of tricyclopentanoids which is continuing unabated.[1-5] Capnellene **1**, a tricyclopentanoidal sesquiterpene isolated from the marine soft coral *Capnella imbricata* is one of the most popular targets for synthesis[4,5] presumably because of its molecular architecture, disposition of methyl groups, exocyclic olefinic linkage and its role in the defence mechanism and biosynthesis[3a] of oxygenated capnellenes. However, most of the syntheses of capnellene generate its tricyclic framework iteratively after a long multistep sequence often in a nonstereoselective fashion.

We wish to delineate herein, a total synthesis of capnellene **1** (Fig.1) from p-cresol and cyclopentadiene. The key features of the synthesis are inverse demand Diels-Alder reaction and oxa-di-π-methane rearrangement.

The cornerstone of our strategy is the recognition of the structural and functional relationship between capnellene **1** and the *endo* annulated tricyclo[5.2.2.$0^{2,6}$]undecenone **4e** *via* the intermediate **5** which was thought to be readily amenable from **4e** by triplet sensitized oxa-di-π-methane rearrangement.[6] Furthermore, the tricyclic system **4e** is related with p-cresol derivative **2b** *via* **4a** which appeared to be easily accessible in a single step from oxidation of **2b** and subsequent interception of the resulting spiroepoxycyclohexa-2,4-dienone **3** (Scheme-1).



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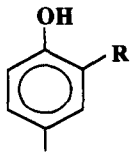
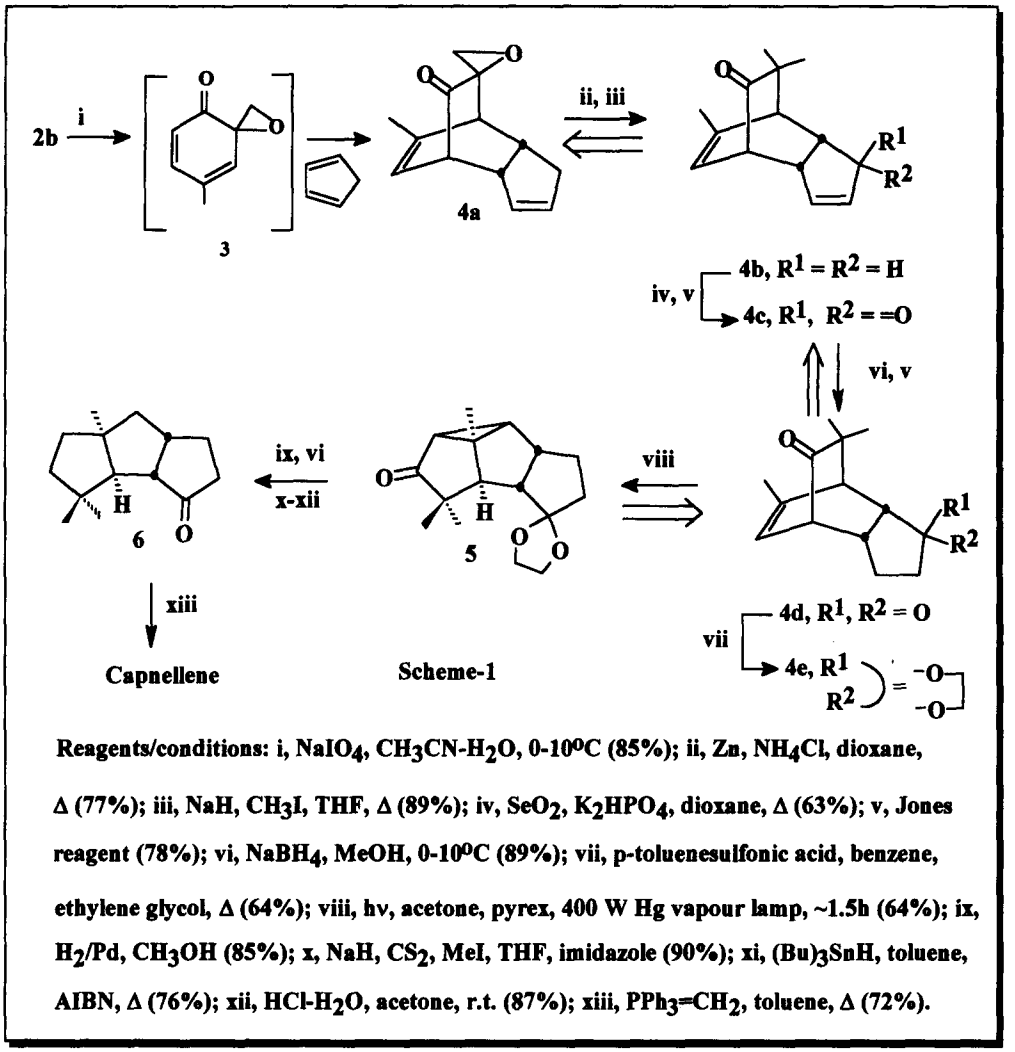


2a, R = H
b, R = CH_2OH

Fig. 1



Reagents/conditions: i, $NaIO_4$, CH_3CN-H_2O, 0-10°C (85%); ii, Zn, NH_4Cl, dioxane, Δ (77%); iii, NaH, CH_3I, THF, Δ (89%); iv, SeO_2, K_2HPO_4, dioxane, Δ (63%); v, Jones reagent (78%); vi, $NaBH_4$, MeOH, 0-10°C (89%); vii, p-toluenesulfonic acid, benzene, ethylene glycol, Δ (64%); viii, hν, acetone, pyrex, 400 W Hg vapour lamp, ~1.5h (64%); ix, H_2/Pd, CH_3OH (85%); x, NaH, CS_2, MeI, THF, imidazole (90%); xi, $(Bu)_3SnH$, toluene, AIBN, Δ (76%); xii, HCl-H_2O, acetone, r.t. (87%); xiii, $PPh_3{=}CH_2$, toluene, Δ (72%).

There are several noteworthy features of the present strategy. For example, the thirteen (out of fifteen) carbon atoms of capnellene are derived from the aromatic precursor **2b**, and cyclopentadiene and assembled in a single step to form the tricyclic system **4a**. Remarkably all the three *cis:anti:cis* fused five membered rings, angular and one of the geminal methyl groups of capnellene are contained in the adduct **4a** in latent form. Transformation of the oxirane moiety of the tricyclic system **4a** into geminal dimethyl group and functionalisation of the five membered ring generates the chromophoric system **4e** endowed with all the stereochemical and functional features of capnellene. Moreover the photochemical reorganisation of **4e** into the tetracyclic intermediate **5** with desired stereochemical disposition of rings, substituents and functonal groups in a single stereoselective sequence is another novel feature of our plan.

Thus, the p-cresol analogue **2b** was readily prepared by controlled hydroxymethylation of p-cresol and subjected to oxidation with sodium metaperiodate in aqueous acetonitrile containing cyclopentadiene to give the ketoepoxide **4a** in excellent yield (85%) following a procedure developed in our laboratory.[6d] The structure and stereochemistry of the adduct **4a** was deduced from its high field (300 MHz) ^{1}H NMR, ^{13}C NMR and COSY analysis. Reductive deoxygenation[7] of **4a** with Zn in dry dioxane containing ammonium chloride followed by alkylation of the resulting compound, with methyl iodide in the presence of NaH-THF gave the dimethyl compound **4b**. Thus, the fourteenth carbon atom (methyl of the geminal methyl group) was also installed on the adduct **4a**. The allylic oxidation of the five membered ring of **4b** with SeO_2 and subsequent oxidation of the resulting alcohol with Jones reagent gave the enone **4c**, thus the functionality at C-5 (equivalent to C-9 of the capnellene) was also introduced rapidly and efficiently. Selective reduction of (both 1,4 and 1,2) of the enone group with sodium borohydride[8] at ~10°C followed by oxidation with Jones reagent furnished the diketone **4d** in good yield (61%). The selective protection of the cyclopentanone carbonyl with ethylene glycol in the presence of p-toluenesulfonic acid gave the desired precursor **4e**.

Towards synthesis of capnellene, the tricyclic chromophoric system **4e** was irradiated in acetone (both solvent and sensitizer) with a mercury vapour lamp (400 W, Applied Photophysics) for about 1.5h. Removal of solvent under vacuum followed by a careful chromatography of the photolysate furnished the rearranged product **5** in good yield (64%). Reductive cleavage[9] of the peripheral cyclopropane bond with H_2/Pd and deoxygenation of the carbonyl group by Barton's method and hydrolysis of the ketal gave the intermediate **6**, whose structure was clearly revealed from its spectral data and comparison.[10] Finally, the Wittig reaction on **6** with triphenylphosphonium methylide generated the natural product capnellene **1**, whose structure was clearly revealed from its high field (300 MHz) ^{1}H NMR, ^{13}C NMR spectra[11] and comparison of its spectral features with those reported.[4a]

In summary, we have developed a conceptually novel synthesis of capnellene from p-cresol and cyclopentadiene. It constitutes a rare example which is equivalent to opening of an aromatic ring 'and restiching with cyclopentadiene to give the thirteen carbons of capnellene with appropriate connectivity and stereochemical orientation. Addition of two more carbons at appropriate junctures completed the synthesis. Moreover simplicity of the reagents and conditions are other noteworthy features of the synthesis.

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11. Data of **1**: IR (Neat) ν_{max} : 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ, 4.85 (br m, 1H, olefinic H), 4.79 (br m, 1H, olefinic H), 2.70-2.3 (complex multiplets, total 4H), 1.8-1.64 (m, 3H), 1.56-1.42 (m, 5H), 1.20 (dd, J_1=~13 Hz, J_2=~9.5 Hz, 1H), 1.15 (s, 3H, CH_3), 1.06 (s, 3H, CH_3) and 0.98 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.04, 69.13, 52.35, 47.96, 46.07, 41.74, 40.63, 31.89, 31.58, 30.88, 29.11, 26.12 (quaternary carbons not shown). Mass (m/z): 204 (M^+). These spectral features are in good agreement with those reported in the literature.[4a]

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