The Total Synthesis of (+)-Norpatchoulenol: Trapping of a Non-enolizable 1,3-Diketone Intermediate with a Wittig Reagent

Hsing-Jang Liu* and Milan Ralitsch

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

A short total synthesis of (+)-norpatchoulenol (**1**) has been accomplished from (+)-camphor-10-sulphonic acid (**2**) involving, as a key step, the trapping of a non-enolizable 1,3-diketone intermediate with a Wittig reagent.

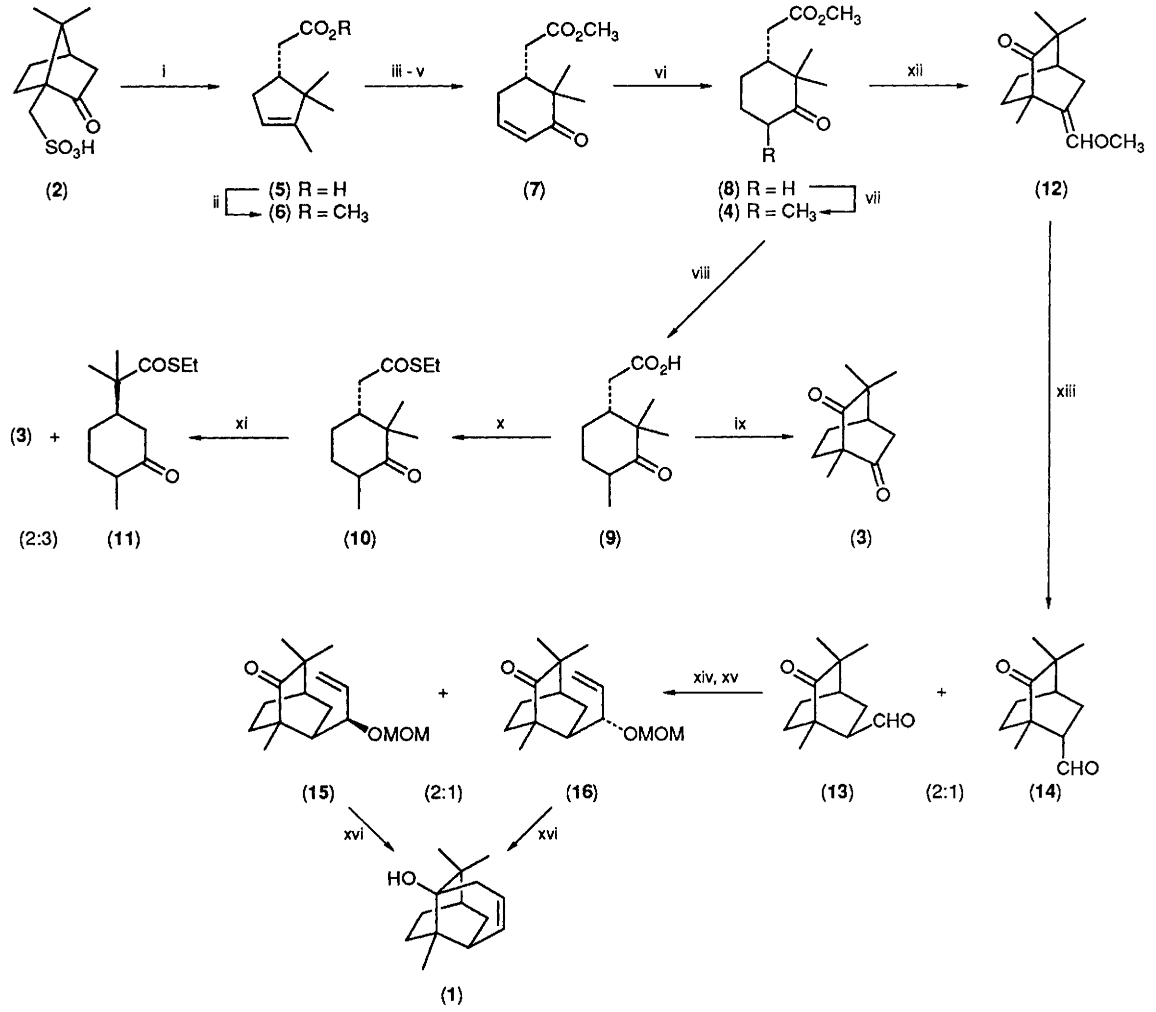
Patchouli oil has been used as a raw material in the perfume industry for over 100 years. In 1973, Teisseire *et al.* reported[1,2] the isolation of a nor-sesquiterpene alcohol, which has the characteristic scent of the oil. This minor constituent, which was named as (+)-norpatchoulenol, was found to possess the structure and absolute configuration depicted in formula (**1**).[3—5] Extensive studies on the synthesis of this interesting natural alcohol have resulted in the preparation of its racemic modification,[6—9] its (−)-antipode *via* a resolution process,[8,10] and a deoxy derivative.[11] Herein, we describe a short synthesis of norpatchoulenol in its natural (+)-form, starting from readily available (+)-camphor-10-sulphonic acid (**2**).

A retrosynthetic analysis suggests that diketone (**3**) is a potentially useful synthetic precursor, which can be converted into the target molecule by inserting a propenyl unit between the two carbonyl groups. Diketone (**3**) could, in principle, be prepared from (+)-camphor-10-sulphonic acid (**2**) *via* the intermediacy of keto ester (**4**) as follows. Heating of acid (**2**) and potassium hydroxide at *ca.* 400 °C,[12] followed by methylation of the resulting (+)-campholenic acid (**5**) with potassium carbonate and methyl iodide in acetone[13] gave rise to (+)-methyl campholenate (**6**).† This ester was subjected to ozonolysis at −78 °C in methanol–dichloromethane. Reductive work-up using triphenylphosphine,[15] followed by treatment of the crude keto aldehyde thus formed with toluene-*p*-sulphonic acid (*p*-TsOH) in refluxing benzene afforded enone ester (**7**). Hydrogenation of (**7**) using 5% palladium on carbon as a catalyst gave keto ester (**8**). A number of conditions were tested for the introduction of a single methyl group to this compound. The best results were obtained when the reaction was carried out at −78 °C with a large excess of methyl iodide (6 equiv.) using potassium hexamethyldisilazide (KHMDS) as a base. Under these conditions, the desired keto ester (**4**) was obtained in good yield without apparent formation of the dimethylation product.

Several methods were examined for the cyclization of keto ester (**4**) to the desired dicarbonyl intermediate (**3**). Initially,

---

† This compound showed a specific rotation $[\alpha]_D^{22}$ +12° (*c* 1.0, $CHCl_3$) and an enantiomeric excess (e.e.) of >99% as determined by Mosher's method[14] using the corresponding alcohol.



Scheme 1. *Reagents and conditions*: i, KOH, ~400 °C, 80%; ii, K_2CO_3, MeI, acetone, 20 °C, 98%; iii, O_3, CH_2Cl_2, MeOH, −78 °C; iv, Ph_3P; v, *p*-TsOH, C_6H_6, reflux, 80% (**6** → **7**); vi, H_2, Pd/C, EtOAc, 20 °C, 97%; vii, KHMDS, MeI, dimethoxyethane (DME), −78 °C, 77%; viii, LiI, pyridine, H_2O, reflux, 88%; ix, PPA, AcOH, 100 °C, 25%; x, $PhOPOCl_2$, EtSH, pyridine, CH_2Cl_2, 20 °C, 99%; xi, LDA, tetrahydrofuran (THF), −78 °C, 37%; xii, KH, DMSO, $Ph_3P{=}CHOMe$, C_6H_6, 20 °C, 52%; xiii, 35% aq. $HClO_4$, Et_2O, 20 °C, 95%; xiv, $CH_2{=}CHLi$, THF, −78 °C, 87%; xv, NaH, MOMCl, DME, 20 °C, 97%; xvi, Na, THF, reflux, 10—15%.

direct cyclization of (**4**) was attempted using potassium hydride, potassium hexamethyldisilazide, or lithium di-isopropylamide (LDA) as a base. However, under no conditions applied could the desired product be obtained. In another method, ester (**4**) was converted to the corresponding carboxylic acid (**9**) with lithium iodide in refluxing pyridine.[16] This acid could be cyclized to diketone (**3**) by treatment with polyphosphoric acid (PPA) and acetic acid at 100 °C,[17,18] but in poor yield (25%). The cyclization of keto thiolester (**10**) was also explored. The compound was readily prepared from acid (**9**) by treatment with phenyl dichlorophosphate, ethanethiol, and pyridine.[19] Compound (**10**) was found to undergo cyclization readily at −78 °C, using lithium di-isopropylamide as a base. However, the desired diketone was again formed in low yield (15%). Interestingly, a substantial amount (22%) of keto thiolester (**11**) was also produced. This compound was apparently formed by the ring opening of diketone (**3**). Such a facile cleavage of the non-enolizable 1,3-diketone could account for the poor results so far obtained. One potential solution to this problem was to trap the apparently unstable diketone intermediate with a suitable reagent. A Wittig reagent was attractive, as it should sustain the reaction conditions and, at the same time, could provide additional carbon units towards the completion of the synthesis. Thus, keto ester (**4**) was treated with potassium hydride and preformed methoxymethylenetriphenylphosphorane in dimethyl sulphoxide (DMSO) and benzene at room temperature. To our delight, a 52% yield of the desired enol ether (**12**) was formed. Hydrolysis of (**12**) with perchloric acid gave a separable mixture of keto aldehydes (**13**) and (**14**) in 2 : 1 ratio. The latter isomer could be epimerized to (**13**) by kinetic protonation.[10]

Racemic keto aldehyde (**13**), previously prepared by Teisseire *et al.* using a different route, had been transformed to (±)- and (−)-norpatchoulenol.[8,10] A similar sequence was applied to effect the conversion of the optically active keto aldehyde (**13**) to (+)-norpatchoulenol. Thus, addition of vinyl-lithium to (**13**), followed by treatment of the resulting epimeric alcohols with sodium hydride and chloromethyl methyl ether (MOMCl), gave rise to separable keto ethers

(**15**) and (**16**) (2 : 1). These epimers were individually cyclized with sodium in tetrahydrofuran to give (+)-norpatchoulenol.‡ The synthetic material thus obtained showed physical properties {^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddd, 1H, *J* 3.0, *J'* 6.0, *J''* 10 Hz, –C*H*=CH–), 5.49 (ddd, 1H, *J* 2.0, *J'* 5.0, *J''* 10 Hz, –CH=C*H*–), 2.38 (dd, 1H, *J* 4.5, *J'* 18 Hz), 1.85—1.55 (m, 3H), 1.50—1.30 (m, 3H), 1.10 (s, 6H, Me), and 0.81 (s, 3H, Me); IR ($CHCl_3$ cast film) 3620 (free OH), 3500 (bonded OH), and 1650 cm^{-1} (C=C); M^+ *m/z* 206.1675 (calc. 206.1671); $[\alpha]_D^{22}$ +42° (*c* 0.26, MeCN)} in good agreement with those reported for the natural material.[3,4]

We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support and the Alberta Heritage Foundation for Medical Research for a Studentship to M. R.

Received, 6th March 1990; Com. 0/00991A

References

1 P. Teisseire, *Riv. Ital. Essence, Profumi, Piante Off., Aromi, Saponi, Cosmet., Aerosol*, 1973, **55**, 572.
2 P. Teisseire, P. Maupetit, and B. Corbier, *Recherches*, 1974, **19**, 8.
3 P. Teisseire, P. Maupetit, B. Corbier, and P. Rouillier, 6th Int. Congr. Ess. Oils (papers), 1974, Paper No. 165.
4 P. Teisseire, P. Maupetit, B. Corbier, and P. Rouillier, *Recherches*, 1974, **19**, 36.
5 W. E. Oberhänsli and P. Schönholzer, *Recherches*, 1974, **19**, 62.
6 P. Teisseire, P. Pesnelle, B. Corbier, M. Plattier, and P. Maupetit, *Recherches*, 1974, **19**, 69.
7 W. Oppolzer and R. L. Snowden, *Tetrahedron Lett.*, 1978, 3505.
8 M. Bertrand, P. Teisseire, and G. Pélerin, *Tetrahedron Lett.*, 1980, **21**, 2051.
9 H. Niwa, T. Hasegawa, N. Ban, and K. Yamada, *Tetrahedron Lett.*, 1984, **25**, 2797.
10 M. Bertrand, P. Teisseire, and G. Pélerin, *Nouv. J. Chim.*, 1983, **7**, 61.
11 J.-L. Gras, *Tetrahedron Lett.*, 1977, 4117.
12 R. S. Sauers, *J. Am. Chem. Soc.*, 1959, **81**, 925.
13 H. J. Liu and P. C. L. Yao, *Can. J. Chem.*, 1977, **55**, 822.
14 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
15 O. Loreny and C. R. Parks, *J. Org. Chem.*, 1965, **30**, 1976.
16 F. Elsinger, J. Schrieber, and A. Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113.
17 H. Gerlach and W. Müller, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 1030.
18 J. A. Oplinger and L. A. Paquette, *Tetrahedron Lett.*, 1987, **28**, 5441.
19 H. J. Liu and S. I. Sabesan, *Can. J. Chem.*, 1980, **58**, 2645.

---

‡ The yields were considerably lower than those reported,[8,10] most likely owing to the much smaller reaction scale.