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KETONE METHYLENATION WITHOUT EPIMERIZATION: TOTAL SYNTHESIS OF (±) LAURENE

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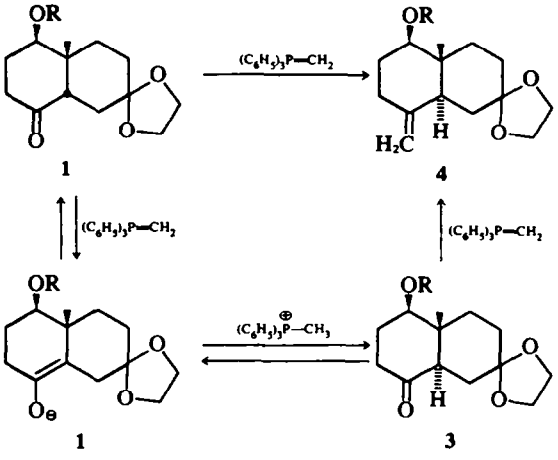
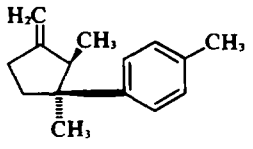
Abstract—A total synthesis of the sesquiterpene hydrocarbon laurene, incorporating a non-epimerizing method of ketone methylenation, has been achieved. It is shown that both the phosphonic acid bis(dimethylamide) method of Corey and Kwiatkowski and the phosphite pyrolysis method of Kuwajima are non-epimerizing. For the present case however, the recently published method of Coates [*J. Am. Chem. Soc.* **94**, 4758 (1972)] is preferable.

The Wittig reaction for the conversion of carbonyl compounds to olefins is one of the more useful transformations in organic chemistry.[1] Its generality is in one way limited however by the fact that the Wittig phosphorane, in addition to being a nucleophile, is also a strong base which can epimerize an asymmetric center α to the carbonyl. To choose one recent example from the literature, Heathcock has reported[2] the following:



The phosphorane deprotonates ketone **1** to form enolate **2** plus phosphonium ion. Reversal can then lead either to starting ketone **1** or epimer **3**. If this epimerization is fast compared to olefination, and if the rates of olefination of both ketones are similar, then the olefin product (**4**) will be derived largely from the more stable ketone (**3**).

Another such example was reported[3] by Irie in connection with his work on laurene, a sesquiterpene hydrocarbon which he had isolated from the algae *Laurencia glandulifera* Kützing and for which he had proposed structure **5**.



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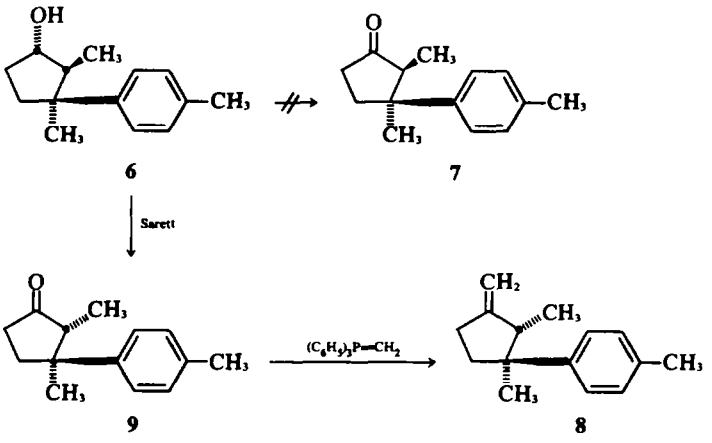
An important factor in Irie's stereochemical assignment was the unusually high field Me doublet occurring at $\delta = 0{\cdot}68$ in the NMR spectrum of laurene. This was interpreted as being a result of the *cis*-1,2 relationship of the secondary Me with the *p*-tolyl group. Models clearly show the Me group lying within the shielding cone of the aromatic ring.

In an attempted total synthesis of laurene, alcohol **6** was prepared (methyl doublet $\delta = 0{\cdot}62$) and oxidized by Sarett reagent to yield a ketone (Me doublet $\delta = 0{\cdot}96$) assumed to be **7**. Wittig olefination of "**7**" however, gave, not laurene, but an isomer which was shown to be epilaurene (**8**) (Me doublet $\delta = 0{\cdot}92$). Thus again an epimerization seems to have occurred during a Wittig reaction.

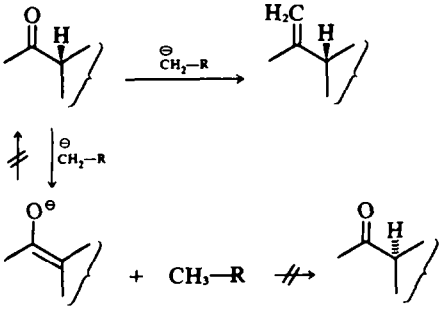
On reading Irie's paper, we were disturbed by the rather low field NMR position of the doublet Me reported for **7** ($\delta = 0{\cdot}96$). It seemed to us quite likely that Sarett oxidation of **6** (overnight in excess pyridine) had in fact yielded the already epimerized ketone **9** and that Wittig olefination then proceeded "normally".

This did in fact prove to be the case (*vide infra*) but we recognized nevertheless that a need existed for an olefin synthesis which would not cause epimerization. We therefore began a search for such a method with the intention of synthesizing laurene as a demonstration of utility, and of clarifying a possible error in the literature.

One approach to the problem is to seek a reagent which is a good nucleophile but which also has a basicity much greater than that of a normal enolate



ion. If the reagent does deprotonate the ketone, the reprotonation to give epimer would be energetically highly unfavorable. The enolate might then be effectively removed from consideration until work-up. With this approach, the yield of olefin product might be diminished due to competing enolization, but the substrate would at least be stereochemically unmolested.



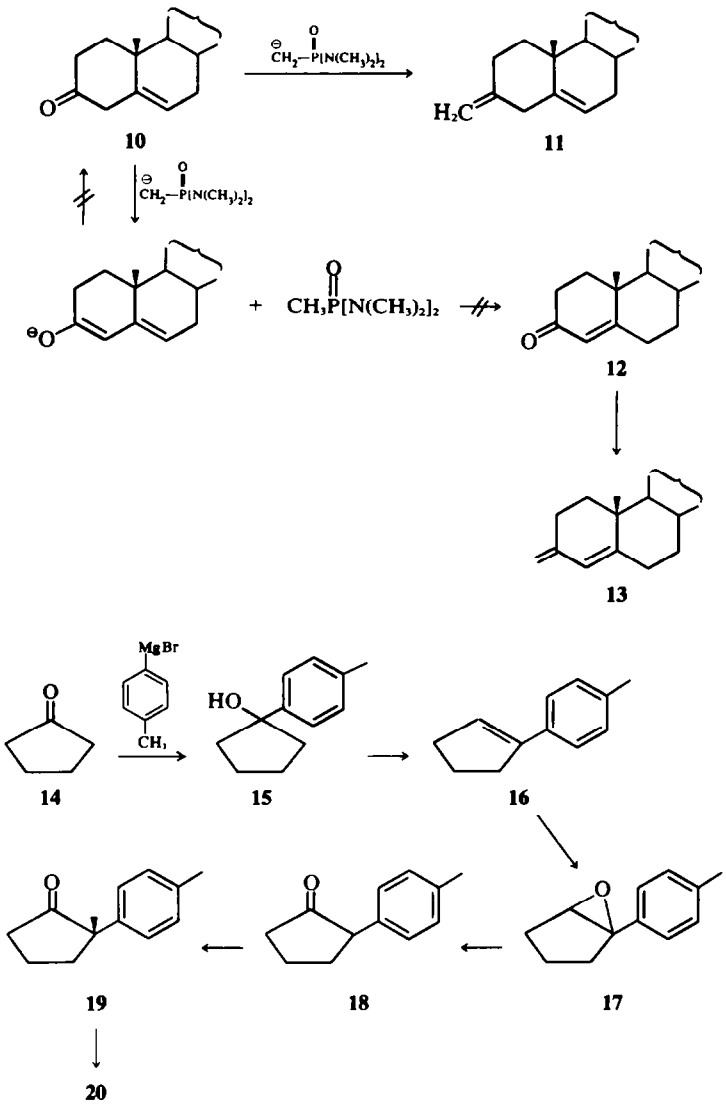
Discovered by Corey in 1966, α-lithio methylphosphonic acid bis(dimethylamide)[4] is a reagent which might meet the necessary specifications. A hint of this can be found in the report[5] that reaction of α-lithio ethylphosphonic acid bis(dimethylamide) with acetophenone gives much starting material on work up, as well as adduct. One explanation of these results is that some acetophenone is enolized and not reprotonated during the reaction, then is recovered on work up.

In order to test these ideas, we treated Δ^5-cholesten-3-one (**10**) both with excess α-lithio methyl phosphonic acid bis(dimethylamide) according to Corey's procedure,[5] and with the normal Wittig reagent.[6] Treatment with methylene triphenylphosphorane in DMSO gave conjugated diene **13** as the major olefinic product (61%). The product mixture from the Corey reagent however consisted largely of a mixture of Δ^4 and Δ^5 cholestenones along with 3-methylene-Δ^5-cholestene (**11**) as the sole olefinated product in 20% yield. None of the conjugated diene **13** was detected.

We therefore concluded that our assumptions were valid and that the Corey olefination method is "non-epimerizing". In the particular case of **10**, it is unfortunate that enolization predominates over addition to such a large extent, but this is presumably a reflection of the increased acidity of a β,γ-unsaturated ketone *vs* a normal saturated ketone, and the method might be expected to work well in other cases.

Our synthesis of laurene was planned to follow the general outline of Irie's approach,[3] for we felt that oxidation of **6** under mild conditions (Collins reagent) should give the true **7** which we could then olefinate. Cyclopentanone was therefore treated with *p*-tolylmagnesium bromide in ether at 0° followed by two phase hexane-aqueous H_2SO_4 dehydration of the adduct. *p*-Tolylcyclopentene was then epoxidized by treatment with *m*-chloroperbenzoic acid in chloroform, and the labile product was immediately rearranged to 2-*p*-tolylcyclopentanone (**18**) by brief acid treatment. Methylation (NaH/CH_3I) proceeded smoothly followed by addition of methyllithium and acid-catalyzed dehydration to yield the olefin (**21**). Hydroboration–oxidation occurred from the less hindered side to give alcohol **6** along with its isomer **22** in an 8:2 ratio. Oxidation of the alcohol mixture with Collins reagent[7] (room temp, 15 min) gave an 8:2 mixture of the two ketones **7** and **9**. As expected, authentic **7** did in fact show a high field methyl doublet at $\delta = 0{\cdot}76$. These transformations are summarized in Scheme 1.

With authentic **7** available, we attempted the Corey olefination procedure under a variety of conditions, but in all cases epimerized ketone **9** was the sole product obtained, and no olefin was observed. In one experiment, the reaction was quenched by addition of D_2O, and the NMR of the product obtained showed incorporation of deuterium at C2 in **9**.

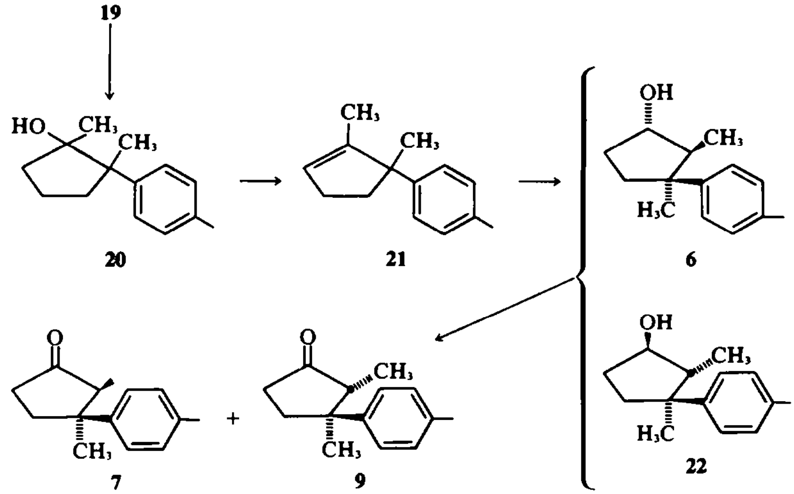


Enolization rather than addition was obviously the sole reaction occurring, so an alternative olefination method was needed.

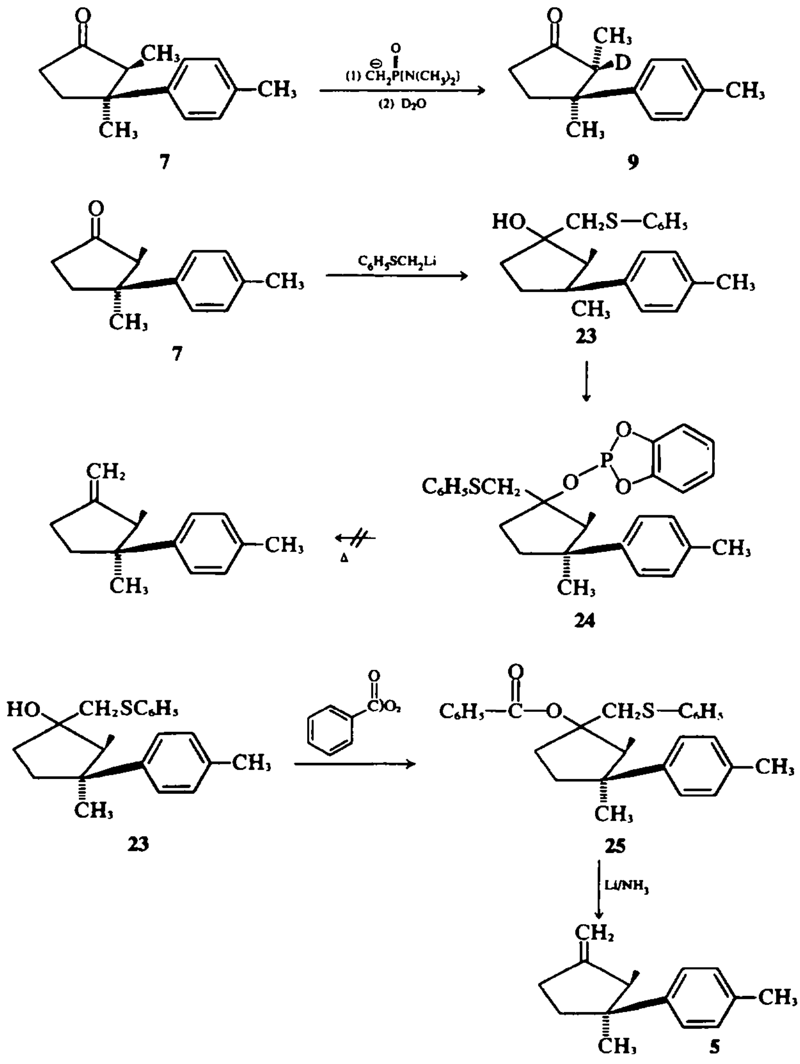
A further olefination method which appeared to meet our specifications is that of Kuwajima[8] in which the adduct obtained by treatment of a ketone with phenylthiomethyllithium is treated with *o*-phenylenephosphorochloridite followed by pyrolysis. Should competing enolization occur, the enolate would not be basic enough to deprotonate thioanisole, so epimerization could not take place. When **7** was treated with phenylthiomethyllithium in THF, a 54% yield of the desired adduct (**23**) was obtained. Formation of the phosphite **24** also occurred normally but **24** could not be induced to undergo thermal elimination to laurene.

At this point, a paper appeared by Coates[9] detailing another method of olefination which was non-epimerizing. Application of the method to laurene proved successful. Treatment of adduct **23** with benzoic anhydride followed by lithium–liquid ammonia reduction of ester **25** according to Coates' conditions proceeded smoothly to give (±) laurene whose spectral properties (IR, NMR, MS) were identical to those published.[3]

In conclusion, we have cleared up a literature error regarding the stereochemistry of ketone **7** and have shown that, although of limited utility, both the methods of Corey and of Kuwajima are non-epimerizing olefinations. It is clear however that the method of Coates is the best procedure for readily enolizable ketones.


19
20
21
6
22
7
9

SCHEME 1


7
9
(1) CH2P(N(CH3)2)2
(2) D2O
C6H5SCH2Li
23
24
25
Li/NH3
5

EXPERIMENTAL

3-Methylene-Δ⁵-cholestene (**11**). A soln of α-lithiomethylphosphonic acid bis(dimethylamide) was prepared by dissolving methylphosphonic acid bis(di-methylamide)[10] (1·41 g, 9·40 mmol) under N_2 in 15 ml dry THF at −78° and adding n-BuLi (4·10 ml of 2·4M soln, 9·80 mmol). After stirring for 30 min, a soln of Δ⁵-cholesten-3-one[11] in 15 ml THF was added and the reaction was warmed to room temp. The reaction was stirred 3 days at 25° and 6 h at 60°, then diluted with water and extracted with ether. The ether extracts were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in 35 ml toluene along with 3 g Florisil, and refluxed under N_2 for 40 h. The solvent was removed under vacuum to give 1·06 g oily residue which was chromatographed on basic alumina. Elution with hexane gave diene **11** (0·325 g, 22%) as a white solid; m 108–110, lit[12] 109–110°. Further elution with ether gave a mixture of conjugated and unconjugated ketones as judged by IR.

1-p-Tolylcyclopentene (**16**). *p*-Tolylmagnesium bromide was prepared in the standard fashion at 0° from Mg turnings (12·2 g, 0·5 mol) and *p*-bromotoluene (63·5 g, 0·37 mol) in 300 ml dry ether. To this soln at 0° was added cyclopentanone (31·1 g, 0·37 mol) in 100 ml ether. The mixture was refluxed for 3 h, then poured onto 500 g crushed ice. After acidification with NH_4Cl, the organic layer was drawn off, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the crude alcohol **15**.

This crude material was dissolved in 500 ml hexane at 0°, and added to a chilled soln of 200 ml 50% H_2SO_4 aq. After stirring for 15 min, the hexane layer was drawn off, washed with sat $NaHCO_3$ and with brine, dried (Na_2SO_4), filtered, and concentrated. Distillation of the residue gave pure olefin **16** (43·3 g, 74%): IR (CCl_4) 3095, 3060, 3040 cm^{-1}; NMR (CCl_4) δ 6·94 (m, 4H), 5·87 (m, 1H), 2·20 (s, 3H); $b_{0.01mm}$ 87–89°.

2-p-Tolylcyclopentanone (**18**). *p*-Tolylcyclopentene (43·3 g, 0·274 mol) was dissolved in 200 ml chloroform at 0°, and a soln of *m*-chloroperbenzoic acid (56·6 g, 0·30 mol) in 500 ml chloroform was added over a 1 h period. After 1 h reaction, the chloroform soln was washed with NaOH aq and with water. The soln was then shaken for 4 min with 300 ml of 20% H_2SO_4 aq to effect rearrangement of the epoxide. The chloroform layer was drawn off, washed with sat $NaHCO_3$ and with brine, then dried (Na_2SO_4), filtered, and concentrated. Distillation of the residue from a trace of $KHSO_4$ gave pure **18** (40·4 g, 85%): IR (neat) 1730 cm^{-1}; NMR (CCl_4) δ 6·97 (s, 4H), 2·30 (s, 3H); b_{1mm} 105°.[13]

2 Methyl-2-p-tolylcyclopentanone (**19**). A soln of **18** (40·4 g, 0·23 mol) in 100 ml dry glyme was added to a cold suspension of sodium hydride (11·5 g of 50% dispersion in mineral oil; 0·24 mol) in 200 ml dry glyme. After H_2 evolution had ceased, MeI (106 g, 47 ml, 0·75 mol) was added over 30 min and the reaction was allowed to stand overnight at room temp. Excess MeI was removed by evaporation at 40°, and the residue was taken up in ether–water. The organic layer was drawn off, washed with brine, dried (Na_2SO_4), filtered, and evaporated to give **19** (40·69 gm, 93%): IR (neat) 1740 cm^{-1}; NMR (CCl_4) δ 7·04 (m, 4H), 2·26 (s, 3H), 1·27 (s, 3H).[13]

2,3-Dimethyl-3-p-tolylcyclopentene (**21**). A soln of **19** (40·0 g, 0·212 mol) in 250 ml ether was added dropwise to a stirred soln of MeLi (110 ml of 2·0M soln, 0·22 mol) in 250 ml ether at 0°. The reaction was stirred for 36 h at room temp, then quenched by slow, cautious addition of NH_4Cl aq. The ether layer was drawn off, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in 500 ml MeOH and 50 ml con HCl was added. After refluxing for 2 h, the soln was neutralized with 10% NaOH aq, diluted with 300 ml water, and extracted (3 × 100 ml) with pentane. The extracts were combined, washed with brine, dried (Na_2SO_4), filtered, concentrated, and distilled to give olefin **21** as a colorless oil (22·4 g, 57%): NMR (CCl_4) δ 7·01 (s, 4H), 5·41 (m, 1H), 2·26 (s, 3H), 1·43 (s, 3H), 1·38 (s, 3H): b. 0·14 mm 56–58°.[13]

2,3-Dimethyl-3-p-tolylcyclopentanol (**6**). A soln of borane in THF (12 ml of 1·0M soln) was added to a soln of **21** (3·3 g, 0·018 mol) in 100 ml dry THF, and the reaction stirred for 3 h at room temp. Water (12 ml) was cautiously added, followed by 30% H_2O_2 (20 ml) and 10% NaOH (20 ml). The reaction was heated to 45° for 1 h then cooled, diluted with water, and extracted with ether. The extracts were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatography of the residue on silica gel gave 2·61 g of alcohol mixture along with 0·46 g recovered **21**. The alcohol mixture consisted of the two compounds **6** and **22** in an 4:1 ratio as estimated by NMR. Alcohol **6** had the following spectral properties: IR (neat) 3345 cm^{-1}; NMR (CCl_4) δ 6·97 (s, 4H), 2·27 (s, 3H), 1·38 (s, 3H), 0·48 (d, 3H, J = 7 Hz).[13]

2,3-Dimethyl-3-p-tolylcyclopentanone (**7**). A 4:1 mixture of alcohols **6** and **22** (4·5 g, 22·0 mmol) in 100 ml dry CH_2Cl_2 was added to a soln of Collins reagent prepared from CrO_3 (15·4 g, 0·153 mol) and pyridine (24·3 g, 0·31 mol) in 400 ml CH_2Cl_2.[14] After 10 min stirring at room temp, the reaction was poured into sat $NaHCO_3$. The CH_2Cl_2 phase was drawn off, washed with cold 1N HCl to remove pyridine, washed with $NaHCO_3$ and brine, then dried (Na_2SO_4), filtered, and concentrated to give 4·26 g (96%) of a 4:1 mixture of the two ketones **7** and **9**. Due to the lability of **7**, separation could not be effected by chromatography. Ketone **7** had the following properties: IR (neat) 1740 cm^{-1}; NMR (CCl_4) δ 7·02 (s, 4H), 2·30 (s, 3H), 1·37 (s, 3H), 0·76 (d, 3H, J = 7 Hz).

Attempted Corey olefination of **7**. The 4:1 mixture of ketones **7** and **9** prepared above (100 mg, 0·49 mmol) was dissolved in 1 ml THF and added to a soln of α-lithiomethyl phosphonic acid bis(dimethylamide) 2·45 mmol) in 10 ml THF at −78°. The reaction was stirred 5 h at −78°, 12 h at 25°, and finally refluxed for 4 h. After dilution with water, the reaction was extracted with ether. These extracts were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give an oily product which was spectrally identical to pure **9**: IR (neat) 1745 cm^{-1}; NMR (CCl_4) δ 7·12 (m, 4H), 2·31 (s, 3H), 1·16 (s, 3H), 0·95 (d, 3H, J = 7 Hz).

2,3 - Dimethyl - 3 - (p - tolyl) - 1 - phenylthiomethylcyclopentanol (**23**). Thioanisole (1·24 g, 10·0 mmol) was dissolved in 20 ml dry THF at 0°, n-BuLi (5·20 ml of 1·92M soln, 10·0 mmol) was added, and the mixture was let stir overnight. The 4:1 mixture of ketones **7** and **9** (400 mg, 1·98 mmol) was dissolved in 2·0 ml dry THF at −78°, and a 12 ml aliquot (4·0 mmol) of the phenylthiomethyllithium soln was added. After 6 h stirring at −78°, the reaction was brought to room temp and stirred an additional 12 h. The reaction was then diluted with water and extracted with ether. The ether extracts were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatography of the residue on basic alumina gave 0·36 g (54%) of pure **23**: IR (neat) 3525 cm^{-1}; NMR (CCl_4) δ 7·2–6·8 (m, 9H), 3·06 (s, 2H), 2·29 (s, 3H), 1·37 (s, 3H), 0·52 (d, 3H, J = 7 Hz).

2,3 - *Dimethyl* - 3 - (p - *tolyl*) - 1 - *phenylthiomethylcyclopentanol benzoate* (**25**). Alcohol **23** (515 mg, 1·58 mmol) was dissolved in 10 ml dry THF at − 10° under N_2, and n-BuLi (0·81 ml of 2·3M soln, 1·86 mmol) was added. After stirring for 15 min, benzoic anhydride (679 mg, 3·0 mmol) in 10 ml THF was added, and the reaction let stir 24 h at room temp. The reaction was then diluted with 100 ml pentane, filtered, and concentrated. Chromatography of the residue on silica gel gave 560 mg (82%) of benzoate **25**: IR (neat) 1720 cm^{-1}; NMR (CCl_4) δ 7·6–6·6 (m, 14H), 4·10 (d, 1H, J = 13 Hz), 3·20 (d, 1H, J = 13 Hz), 2·20 (s, 3H), 1·43 (s, 3H), 0·89 (d, 3H, J = 7 Hz).

(±) *Laurene* (**5**). Benzoate **25** (655 mg, 1·52 mmol) in 15 ml ether was added to a refluxing soln of Li (55 mg, 8·0 mmol) in 50 ml liquid NH_3, and the reaction was stirred for 1 h. Pentane (30 ml) was then added and excess Li was quenched by cautious addition of solid NH_4Cl. After evaporation of NH_3, the residue was taken up in pentane–water. The pentane layer was drawn off, washed with 10% NaOH aq and with brine, then dried (Na_2SO_4), filtered, and concentrated. Chromatography of the residue on Florisil[15] gave 163 mg (55%) pure (±) laurene:[13] IR (neat) 1660, 870 cm^{-1}; NMR (CCl_4) δ 6·97 (s, 4H), 4·80 (broad s, 2H), 2·27 (s, 3H), 1·24 (s, 3H), 0·68 (d, 2H, J = 7 Hz). The analytical sample was obtained by preparative VPC on a 20% SF-96 column followed by microdistillation. (Found: C, 89·70; H, 10·22. Calcd for $C_{15}H_{20}$: C, 89·94; H, 10·06%).

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