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Asymmetric Construction of Quaternary Carbons from Chiral Malonates : Total Syntheses of (+)-Epilaurene and (-)-Isolaurene.

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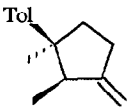
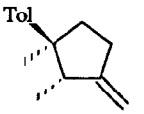
***Abstract** : Enantiomerically pure (+)-epilaurene and (-)-isolaurene were obtained from the chiral malonic acid ester (R)-(+)-4, via the 4-methyl-4-p-tolylhex-5-en-1-al (S)-9 prepared by double Wittig reaction under sonication, which underwent subsequent radical induced cyclization.*

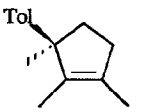
In previous papers we have described the asymmetric construction of quaternary carbons from chiral malonates and the subsequent selective preparations of the two enantiomers of α- and β-cuparenones from a common optically active precursor.[1,2] We report herein the first enantioselective preparations of epilaurene (+)-**2** and isolaurene (-)-**3** from the same single precursor involving a radical cyclization into a five-membered ring.



Laurene
(-)- **1**

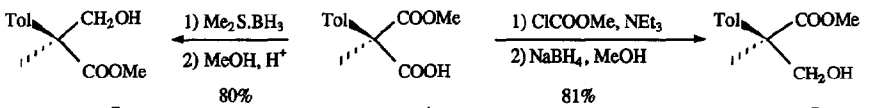


Epilaurene
(+)- **2**



Isolaurene
(-)- **3**

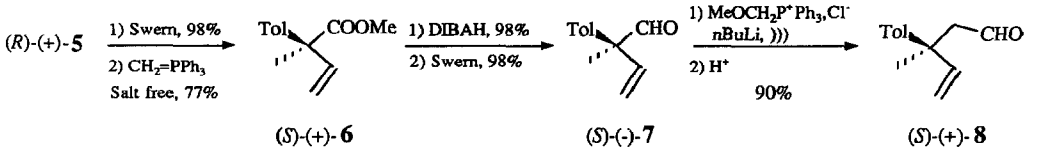
Natural (+)-laurene and (-)-epilaurene were isolated first from *Laurencia glandulifera*, then from several *laurencia* species and more recently from the marine red algae *laurencia elata*. [3] These compounds are the target of many current synthetic efforts, but as far as we know no asymmetric syntheses of these sesquiterpenes have been reported.[4]



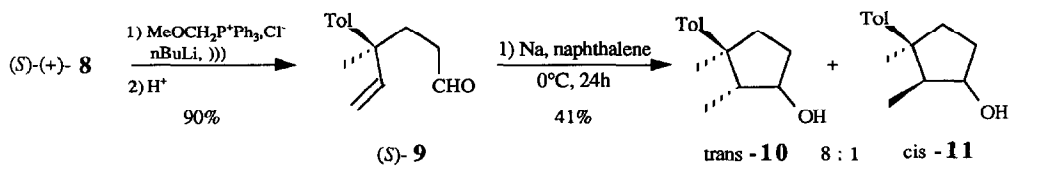
(S)-(-)- **5** (*R*)-(+)- **4** (*R*)-(+)- **5**

We had reported that the malonic acid ester (*R*)-(+)-**4** (≥ 96% ee),[2] readily available from the suitable prochiral dimethyl malonate by enantioselective enzymatic hydrolysis (PLE), underwent reduction either into

the hydroxy ester (*R*)-(+)-**5** (ClCOOMe, NEt_3 then $NaBH_4$) in 81% yield or into its enantiomer (*S*)-(-)-**5** ($Me_2S.BH_3$ and MeOH, $SOCl_2$, 80%), chemoselectively. These chirons (≥ 96% ee) offered valuable and convenient sources of the quaternary stereogenic centers found in sesquiterpenes such as α– and β–cuparenones for instance [1].

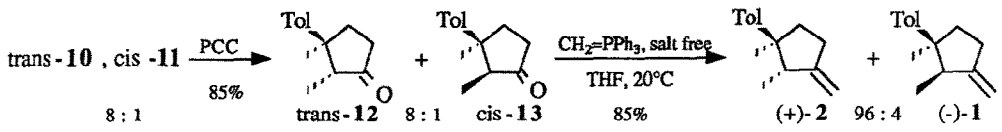


On the other hand , oxidation of the alcohol (+)-**5** (DMSO, $(COCl)_2$ at -60°C then NEt_3, 98%) [5] followed by Wittig olefination with salt free methylene phosphorane (CH_2=PPh_3) [6] gave the corresponding olefin ester (*S*)-**6** ($[\alpha]_D$ = -4.5 , c 1, $CHCl_3$) in 77% overall yield. The conversion of (*S*)-**6** into the aldehyde (*S*)-**7** ($[\alpha]_D$ = -60.8 , c 1, $CHCl_3$)was conveniently achieved by hydride reduction (2 equiv. of DIBAH, CH_2Cl_2, -78°, 98%) and subsequent Swern oxidation (98%). Then homologation [4e,7] of the enal (*S*)-**7** by means of a Wittig reaction with (methoxymethylene)triphenylphosphorus ylide ($Ph_3P^+CH_2OMe,Cl^-$, nBuLi, THF) under sonication [7] provided, after hydrolysis (2N HCl / THF, 1:1), the aldehyde (*S*)-**8** ($[\alpha]_D$ = +5,2 , c 1, $CHCl_3$) in 90% yield.



Further Wittig reaction of the aldehyde **8** with the same ylide, [7] led to a labile enol ether intermediate which, upon hydrolysis with 2N HCl in THF (v/v : 1/1) offered the olefin aldehyde (*S*)-**9** ($[\alpha]_D$ = +13,2 , c 1, $CHCl_3$) in 90% yield and traces (< 5%) of a by-product from transylidation.[7]

The cyclization step was achieved under radical conditions by slow addition of a THF solution of the enal (*S*)-**9** to a freshly prepared THF solution of sodium naphthalenide [8] (6 equiv.) at 0°C within 24 h to provide, at best, 41% yield of a 8:1 mixture of cyclopentanols trans-**10** and cis-**11** besides 20% of dimeric product. Attempts to improve the cyclization yield of enal (*S*)-**9** by using lithium 4,4'-di-*tert*-butylbiphenyl (LiDBB) [9] or with samarium iodide [10] (SmI_2, t-BuOH, -78°C, THF) failed, trans-**10** and cis-**11** were only obtained with 10% and 5% yield respectively, besides alcohol reduction product of (*S*)-**9** (10%) and dimeric product (20-80%). Under the same conditions the cyclization of racemic **9**, was reported to give a 6:1 mixture of racemic cyclopentanols trans-**10** and cis-**11** in 50% yield.[4c]



This 8:1 mixture of alcohols trans-**10** and cis-**11** was oxidized with pyridinium chlorochromate (PCC) [11] dispersed on celite [12] to provide in 85% yield, the key intermediates **12** and **13** as a trans and cis mixture (8:1 ratio from ^{1}H NMR spectra).[13] Wittig reaction of the trans-**12** and cis-**13** (8:1) mixture under standard conditions (CH_2=PPh_3 "salt free", THF, 20°C) furnished after chromatography through alumina [14], a 96:4 mixture of epilaurene (+)-**2** and laurene (-)-**1**, which exhibited spectral data identical with those reported in the literature. [3]

Upon treatment of the 96:4 mixture of trans-**2** and cis-**1** under acidic conditions (SiO_2, H^+, CH_2Cl_2) the isolaurene (-)-**3** was isolated in 85% yield ($[\alpha]_D$ = -109 , c 0.5, $CHCl_3$) (lit. [3a] $[\alpha]_D$ = +108.7 , c 1.4, $CHCl_3$ for its enantiomer). It is noteworthy that the isomerization of trans-**2** into isolaurene (-)-**3** was slower than for laurene cis-**1**. The enantiomeric excess of these compounds [15] was determined from their ^{1}H NMR spectra recorded in the presence of Eu(hfc)$_3$, compared to the corresponding racemic substrates was ≥ 98% ee. In the accompanying paper is reported a new method of determination of the enantiomeric excess of such optically active frameworks based on the 250 MHz ^{2}H NMR spectra of deuterated compounds recorded in Cholesteric liquid crystal media.

In conclusion, from a single chiron (*R*)-(+)-**4** readily available with high enantiomeric purity (≥ 96% ee), we have developed the first asymmetric synthesis of enantiomerically pure epilaurene (+)-**2** and isolaurene (-)-**3** via a double Wittig homologation under sonication and radical cyclization.[16] Moreover isomerization of trans-**12** into cis-**13** (see ref. 13) provide also a way to (-) laurene, as reported with racemic cis-**13**. Furthermore as reported [1,2] from the antipode (*S*)-(-)-**5**, also avaiiable from (*R*)-(+)-**4**, the total syntheses of natural (-)-epilaurene and (+)-isolaurene can be performed following the same sequence.

References and notes

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6) When the Wittig olefination was conducted without salt free reagent the expected olefin **6** was only obtained in 20% yield, besides methyl 2-*p*-tolylpropanoate (degradation product, 80%).

7) Using the conditions previously reported (Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *Chem. Pharm. Bull.* **1985**, *33*, 4821). *c.a.*, reaction of 3 equiv. of $Ph_3P^+CH_2OMe,Cl^-$ with 2.5 equiv. of n-BuLi in THF provided olefin (*S*)-**8** in low yield besides 25-90% yield of a by-product : 3-methyl-3-*p*-tolylocta-1,4-diene. The latter likely arising from butylidenephosphorane which competitively reacts with (*S*)-**7** (for such a transylidation see Seyferth, D.; Hughes, W.B.; Heeren, J.K. *J. Am. Chem. Soc.* **1965**, *87*, 2847, 3467). However, this problem was overcome by using ultrasound to prepare the phosphorane.

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13) Several attempts to isomerize the ketone trans-**12** into cis-**13** under basic conditions ($NaNH_2$ or CH_2=P(O)-$(NMe_2)_2$ [4a] led to 20% and 45% of **13** respectively. Under this latter condition we were not able to obtain pure trans-**12** from the trans-**12** / cis-**13** mixture as reported by McMurry *et al.* [4a]

14) Under the basic conditions of the Wittig reaction, epimerization occurred at C_2 of the cyclopropanone ring, see ref. 4a. ($[\alpha]_D$ = +7.4 , c 1, $CHCl_3$) value of a mixture 96:4 (2*S*,3*S*)-epilaurene **2** and laurene **1**. Compared to the enantiomeric (2*R*,3*R*)-epilaurene (lit. [3a], $[\alpha]_D$ = -3.1 , c 0.5, $CHCl_3$).

15) (a) All new compounds were caracterized by 250 MHz ^1H and ^{13}C NMR, IR, MS and when possible by elemental analysis to ± 0.3%.
(b) (*S*)-(+)-**6**. IR (neat) 1740, 1640 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.16 (s, 4H) ; 6.41 (dd, H_a, J = 11.4 Hz and 17.6 Hz) ; 5.30 (dd, H_b, J = 11.4 Hz and 0.8 Hz) ; 5.16 (dd, H_c, J = 17.6 Hz and 0.8 Hz) ; 3.73 (s, 3H) ; 2.35 (s, 3H) ; 1.65 (s, 3H). ^{13}C NMR ($CDCl_3$) δ : 175.1 (s, C_1) ; 140.9 (d, C_3) ; [6 arom. C : 140.4 (s), 136.3 (s), 129.0 (2d), 126.1 (2d)] ; 114.6 (t) ; 53.3 (s) ; 52.1 (q) ; 23.4 (q) ; 20.8 (q).

(c) (*S*)-(-)-**7**. IR (neat) 1735, 1640 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 9.57 (s, 1H) ; 7.23 (d, J = 7.4 Hz, 2H) ; 7.15 (d, J = 7.4 Hz, 2H) ; 6.24 (dd, H_a, J = 10.3 and 18.2 Hz) ; 5.41 (d, H_b, J = 10.3 Hz) ; 5.19 (d, H_c, J = 18.2 Hz) ; 2.37 (s, 3H) ; 1.55 (s, 3H). ^{13}C NMR ($CDCl_3$) δ : 199.4 (d, C_1) ; 138.4 (d, C_3) ; [6 arom. C : 137.1 (s), 136.8 (s), 129.6 (2d), 127.3 (2d)] ; 117.1 (t) ; 57.4 (s, C_2) ; 20.9 (q) ; 20.0 (q).

(d) (*S*)-(+)-**8**. IR (neat) 1730, 1645 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 9.60 (X part of ABX syst., dd, J_{AX} = J_{BX} = 3 Hz, 1H) ; 7.25 (d, J = 8.8 Hz, 2H) ; 7.17 (d, J = 8.8 Hz, 2H) ; 6.12 (dd, H_a, J = 10.3 and 17.7 Hz) ; 5.22 (dd, H_b, J = 10.3 and 1 Hz) ; 5.13 (dd, H_c, J = 17.2 and 1 Hz) ; 2.79 (AB part of ABX, $\Delta\nu_{AB}$ = 15.8 Hz, J_{AB} = 14.8 Hz, J_{AX} = J_{BX} = 3 Hz, 2H) ; 2.34 (s, 3H) ; 1.55 (s, 3H). ^{13}C NMR ($CDCl_3$) δ : 202.9 (d, C_1) ; 145.1 (d, C_2) ; [6 arom. C : 142.3 (s), 136.1 (s), 129.2 (2d), 126.1 (2d)] ; 112.8 (t, C_5) ; 53.1 (t, C_2) ; 42.4 (s, C_3) ; 26.0 (q) ; 20.8 (q).

(e) (*S*)-(+)-**9**. IR (neat) 1735, 1640 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 9.70 (bs, 1H) ; 7.21 (d, J = 8.0 Hz, 2H) ; 7.13 (d, J = 8.0 Hz, 2H) ; 6.00 (dd, H_a, J = 10.8 and 17.5 Hz) ; 5.15 (dd, H_b, J = 10.8 and 1 Hz) ; 5.08 (dd, H_c, J = 17.5 and 1 Hz) ; 2.50 - 2.25 (m, 2H) ; 2.33 (s, 3H) ; 2.25 - 1.97 (m, 2H) ; 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$) δ : 202.2 (s, C_1) ; 146.0 (d, C_5) ; [6 arom. C : 143.2 (s), 135.6 (s), 129.0 (2d), 126.4 (2d)] ; 112.3 (t, C_6) ; 43.2 (s, C_4) ; 39.8 (t, C_2) ; 32.3 (t, C_3) ; 24.9 (q) ; 20.8 (q).

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(b) This study has been presented to the french Chemical Society meeting (JCO 92) at Palaiseau, France on September **1992**.