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First enantioselective total synthesis of both enantiomers of lancifolol. Correlation: absolute configuration/specific rotation

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Abstract—The first enantioselective total synthesis of both enantiomers of lancifolol has been accomplished using a *Z*-stereoselective Peterson olefination and a palladium-catalyzed cross-coupling reaction as key steps. This approach allows us to correlate the relationship between absolute configuration and specific rotation, to date both unknown.

Lancifolol (*trans*-[2,2,3-trimethyl-4-(4′-methyl-pent-3′-(*Z*)-enylidene)-cyclopentyl]-methanol **1**) is an irregular sesquiterpene alcohol extracted from the roots of *Peucedanum palustre* (L.) Moench (Apiaceae) and *Peucedanum lancifolium* Lange (Apiaceae).[1] This perennial umbellifer grows in wet places, such as swampy meadows, peat bogs, alder forests, and banks of lakes in most parts of Europe extending eastwards to Central Asia. The root, named *Radix Peucedani palustris*, was employed in folk medicine as a remedy against pertussis and spasms.[2] In Slavic countries this root also served as a substitute for ginger, probably because of its pungent and bitter taste.[3] Structural elucidation of lancifolol **1** was carried out mainly by homo- and heteronuclear correlated NMR spectroscopy, but up to now no synthesis of this product has been reported. Moreover, the limited amount of natural material available precluded establishment of the specific rotation.[1]

We report herein the first enantioselective synthesis of both enantiomers of lancifolol. This approach allows us to correlate the relationship between absolute configuration and specific rotation. The correlations thus obtained are expected to be useful for future entire characterization of lancifolol when extracted from other natural sources.

Based on the retrosynthetic analysis depicted in Fig. 1, the final step of our strategy was the palladium-catalyzed cross-coupling reaction of organotin reagents[4] and allylic chlorides[5] or acetates.[6] In attempting to carry out this strategy, the first problem to be encoun-

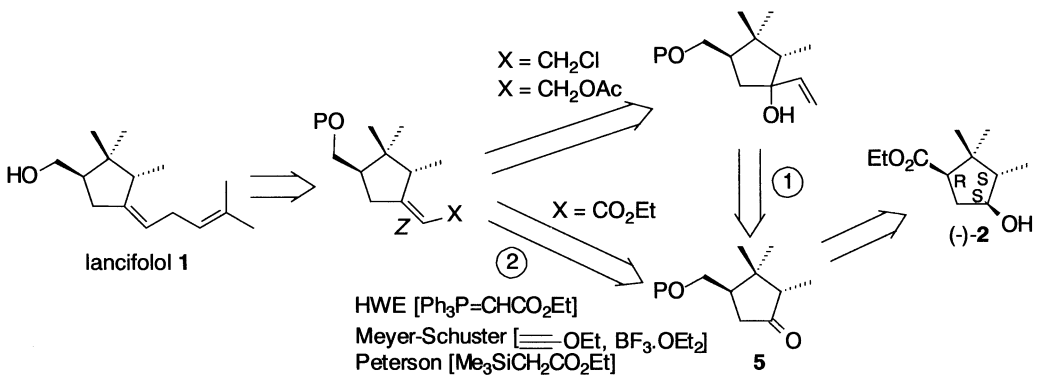

Figure 1. Retrosynthetic analysis of lancifolol **1**.

Keywords: asymmetric synthesis; natural products; stereocontrol; olefination; coupling reactions.

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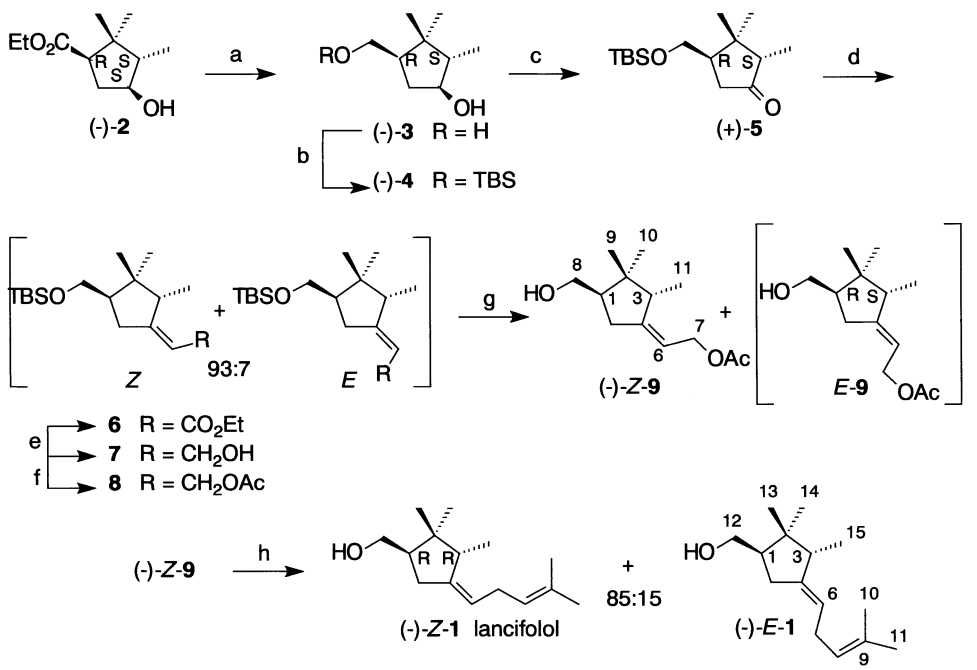
tered was that of *Z*-olefination of the ketone **5** (P= TBS, Fig. 1).

According to the synthetic plan, the starting point of the synthesis was ethyl (1*R*,3*S*,4*S*)-4-hydroxy-2,2,3-trimethylcyclopentane carboxylate (−)-**2** previously prepared in enantiomerically pure form in our laboratory[7] (Scheme 1). Chemoselective protection of the primary hydroxyl group of the corresponding diol (−)-**3** with *t*-butyldimethylsilyl chloride (TBSCl) and imidazole using DMF as a solvent, provided the desired cyclopentanol (−)-**4** in 80% yield, together with the diprotected compound. Careful TLC monitoring of the protection and strict experimental conditions were essential in order to minimize the formation of this by-product.[8] Oxidation of (−)-**4** with catalytic tetrapropylammonium perruthenate (TPAP) and NMO as the co-oxidant in dichloromethane gave (+)-**5** in 95% yield.[9]

With (+)-**5** in hand, we turned our attention to the major problem of the olefination and the evaluation of several issues. In a first attempt, exposure of (+)-**5** to commercially available (carbethoxymethylene)triphenylphosphorane failed (Fig. 1, path 2). The mass balance consisted of recovered partially epimerized ketone, hence the assumption that enolization was the competing process. This failure prompted us to explore alternative strategies and attention was focused on the possibility of employing allylic type rearrangements as a means of access to the requisite functionality. To this end, the reaction of (+)-**5** with the less basic organocerium derivative would be beneficial (Fig. 1, path 1). Indeed, transmetallation of vinyl magnesium bromide with rigorously dried cerium trichloride,[10] followed by reaction with (+)-**5** gave the corresponding tertiary alcohol in excellent yield. Unfortunately, attempts to effect allylic rearrangement to the primary chloride afforded conjugated dienes as sole isolable materials. Moreover, we were unable to synthesize the tertiary allylic acetate in order to perform a palladium-catalyzed sigmatropic rearrangement.[11] A large variety of α,β-unsaturated carboxylic esters have been prepared using the BF_3·etherate-promoted addition of aldehydes and ketones to 1-alkynyl ethers.[12] If the previous approach has been unsuccessful in the rearrangement step, the nucleophilic addition of the organocerium to the carbonyl moiety has been achieved. We therefore turned to the use of acetylene-based nucleophiles and the Meyer–Schuster reaction[13] (Fig. 1, path 2). Simple stirring of (+)-**5** with ethoxyacetylene and BF_3·etherate in dichloromethane at −15°C, furnished the expected esters **6** (49% yield). However, the configuration of the newly generated double bond was a 70:30 mixture of the *E* and *Z* isomers (from ^{13}C NMR, vide infra), which were inseparable.

Encouraged by this result, we continued to try to obtain a higher selectivity and turned our attention to basic conditions. Thus, we have changed to α-silylated esters, which are known to afford ethylenic esters by the Peterson olefination reaction and to be, generally, more reactive than the corresponding phosphorus ylids[14] (Fig. 1, path 2). After several attempts, this method proved the most successful (Scheme 1). Treatment of (+)-**5** in THF with 2 equiv. of ethyl lithiotrimethylsilylacetate (preformed from lithium



Scheme 1. *Reagents and conditions*: (a) $LiAlH_4$, Et_2O, −15°C, 99%; (b) TBSCl, imidazole, DMF, −30°C, 80%; (c) cat. TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 95%; (d) $Me_3SiCH_2CO_2Et$, $(C_6H_{11})2NLi$, THF, −78 to −25°C, 82%; (e) $LiAlH_4$, Et_2O, −15°C, 98%; (f) CH_3COCl, Pyr., Et_2O, rt, 85%; (g) TBAF, THF, rt, 95%; (h) $(Me)_2C{=}CHSnMe_3$, 6 equiv. of LiCl, $Pd(dba)_2$, 0.5% H_2O–DMF, 80°C, 61%.

dicyclohexylamide and ethyl trimethylsilylacetate[14b]) from −78 to −25°C and quenching at this temperature, gave the α,β-unsaturated carboxylic esters **6** in a good chemical yield (82%) and a 93:7 *Z*/*E* ratio diastereoselectivity.† Reduction of the ester moiety with $LiAlH_4$ followed by acetylation of the resulting alcohols **7** using standard procedure (AcCl, Pyr., Et_2O) gave the acetates **8**. Removal of the TBS protecting group of acetates **8** (TBAF, THF) furnished the corresponding derivatives *Z*-**9** and *E*-**9** (93:7 ratio, 95% yield) which were chromatographically separable.[15] Finally, the reaction of *Z*-**9** and isobutenyltrimethyltin[5d] proceeded smoothly and afforded a 61% yield (~22% recovered starting material) of isolated coupling products.[6d] On the basis of the literature data on the palladium-catalyzed cross-coupling reaction between stereodefined allylic acetates and organostannanes,[6d] we expected that this reaction afforded stereoisomerically pure *Z*-**1**. In fact, like reported in one example,[16] this cross-coupling reaction produced a reaction mixture containing compounds *Z*-**1** (lancifolol) and *E*-**1** in a 85:15 molar ratio, respectively. Fortunately, we were able to readily separate these two diastereomers by column chromatography and obtained pure derivatives for the subsequent characterization of lancifolol. The 2D NMR data of our synthetic sample were in complete accord with those of the literature.[1]

In conclusion, (1*R*,3*R*) lancifolol has been synthesized for the first time employing the Peterson olefination as the crucial step in the synthesis. The (1*R*,3*R*) enantiomer is levogyre: $[\alpha]_D^{25} = -13$ (*c* 1.0, $CHCl_3$). The synthetic route that we developed here could also be applied to the synthesis of the enantiomer, starting from (+)-**2**.[7] We think that this work will serve as a basis for the complete characterization of lancifolol, in the event of its isolation in other natural products, simply by the measurement of the specific rotation.

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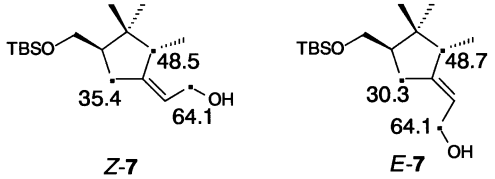
15. All new compounds were fully characterized by IR, ^1H NMR, ^{13}C NMR and 2D NMR.
    Selected analytical data: (−)-*Z*-**9**, $[\alpha]_D^{25} = -40.5$ (*c* 1.0, $CHCl_3$). IR (film): 3400, 3020, 1740, 1237, 1023 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.38 (br tq, 1H, $J = 7.9$, 1.7 Hz, C_6-H), 4.59 and 4.52 (ABX, 2H, $J = 12.3$, 7.9, 7.0 Hz, C_7-H), 3.74 and 3.52 (ABX, 2H, $J = 10.0$, 8.1, 5.3 Hz, C_8-H), 2.70 (br dd, 1H, $J = 16.8$, 8.3 Hz, C_5-H), 2.35 (br q, 1H, $J = 7.4$ Hz, C_3-H), 2.19–2.00 (m, 2H, C_1-H and C_5-H), 2.04 (s, 3H, CH_3-CO), 1.01 (s, 3H, C_9-H or C_{10}-H), 0.93 (d, 3H, $J = 7.4$ Hz, C_{11}-H), 0.77 (s, 3H, C_9-H

† *E*–*Z* configurational assignments of α,β-unsaturated carboxylic esters **6** were derived from that of the corresponding alcohols **7**. Toward this end, esters **6** obtained from Meyer–Schuster (*E* major) and Peterson (*Z* major) reactions were reduced with $LiAlH_4$ and the ^{13}C NMR chemical shifts of each mixture compared (γ-effect).



or C_{10}-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (CO-CH_3), 153.2 (C_4), 115.4 (C_6), 63.9 (C_8), 62.2 (C_7), 48.3 (C_3), 46.3 (C_1), 42.0 (C_2), 34.5 (C_5), 23.3 (CH_3), 23.2 (CH_3), 20.9 (CO-CH_3), 16.4 (C_{11}). Anal. calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.31; H, 9.77.

(−)-*E*-**1**, $[\alpha]_D^{25} = -9$ (*c* 1.0, $CHCl_3$). IR (film): 3364, 3031, 1452, 1023 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ 5.38 (m, 2H, C_6-H and C_8-H), 3.45 and 3.17 (ABX, 2H, $J = 10.3$, 5.4, 8.6 Hz, C_{12}-H), 2.75 (br t, 2H, $J = 7.1$ Hz, C_7-H), 2.46 (br dd, 1H, $J = 17.6$, 8.7 Hz, C_5-H), 2.12 (br d, 1H, $J = 17.3$ Hz, C_5-H), 2.05 (br q, 1H, $J = 6.9$ Hz, C_3-H), 1.72–1.65 (m, 1H, C_1-H), 1.68 (d, 3H, $J = 0.7$ Hz, C_{11}-H), 1.59 (s, 3H, C_{10}-H), 0.88 (d, 3H, $J = 7.0$ Hz, C_{15}-H), 0.79 (s, 3H, C_{13}-H or C_{14}-H), 0.74 (s, 3H, C_{13}-H or C_{14}-H). ^{13}C NMR (125 MHz, C_6D_6): δ 146.3 (C_4), 131.1 (C_9), 123.9 ($C_{vinylic}$), 119.8 ($C_{vinylic}$), 64.0 (C_{12}), 49.0 (C_3), 48.8 (C_1), 42.1 (C_2), 30.9 (C_5), 28.6 (C_7), 25.8 (C_{11}), 23.7 (C_{13} or C_{14}), 23.0 (C_{13} or C_{14}), 17.7 (C_{10}), 14.5 (C_{15}). Anal. calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.74; H, 11.76.

Lancifolol (−)-*Z*-**1**, $[\alpha]_D^{25} = -13$ (*c* 1.0, $CHCl_3$). IR (film): 3350, 3034, 1450, 1023 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ 5.28 (tm, 2H, $J = 7.3$ Hz, C_6-H and C_8-H), 3.47 and 3.25 (ABX, 2H, $J = 10.3$, 5.9, 8.0 Hz, C_{12}-H), 2.81 (br t, 2H, $J = 7.2$ Hz, C_7-H), 2.57 (ddquint., 1H, $J = 16.9$, 7.9, 1.7 Hz, C_5-H), 2.25 (br q, 1H, $J = 7.2$ Hz, C_3-H), 2.00 (ddq, 1H, $J = 16.8$, 10.3, 1.9 Hz, C_5-H), 1.86 (m, 1H, C_1-H), 1.68 (s, 3H, C_{11}-H), 1.60 (s, 3H, C_{10}-H), 0.95 (s, 3H, C_{13}-H or C_{14}-H), 0.93 (d, 3H, $J = 7.3$ Hz, C_{15}-H), 0.75 (s, 3H, C_{13}-H or C_{14}-H). ^{13}C NMR (125 MHz, C_6D_6): δ 145.7 (C_4), 131.0 (C_9), 124.2 ($C_{vinylic}$), 120.9 ($C_{vinylic}$), 64.1 (C_{12}), 48.7 (C_3), 46.9 (C_1), 42.1 (C_2), 34.8 (C_5), 28.7 (C_7), 25.7 (C_{11}), 23.7 (C_{13}), 23.7 (C_{14}), 17.7 (C_{10}), 16.0 (C_{15}). Anal. calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.23; H, 11.77.

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