Lipases-Promoted Enantioselective Syntheses of Monocyclic Natural Products

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Abstract: This review is about using lipases as catalysts in organic synthesis. It provides some specific examples of stereoselective biotransformations used in our group to prepare non racemic chiral building blocks and the utilization of these intermediates to synthesize different target molecules by organic transformations.

Keywords: Lipases, enzymatic resolution, building blocks, natural products, enantioselective syntheses, absolute configurations.

Dedicated to the Emeritus Professor Kenji Mori (The University of Tokyo)

INTRODUCTION

The biological properties of organic molecules depend on their stereochemistry. This is true for drugs, plant growth regulators, flavoring compounds, and all compounds with a biological activity. Nevertheless, in numerous cases, making one diastereomer of a given target by a stereoselective synthesis is not enough. The compound must be a single enantiomer too, with a perfectly determined absolute stereochemistry. Thus, syntheses which secure the building and determination of absolute stereochemistry in the field of natural products are of great interest and they will continue to play a pivotal role. In this context, enzymes have been frequently used as efficient biocatalysts for the asymmetric synthesis of numerous organic compounds. Their greatest advantages are that they do not require any expensive or labile cofactors nor sophisticated recycling technology. This review presents our major works since 1999 in this area. Our plan was to use readily available and easily handled lipases as a tool to provide nonracemic chiral building blocks starting from optically inactive materials and to convert these building blocks to different target molecules by organic transformations. It is presented in two main parts: 1) the enantioselective synthesis of six-membered ring natural products and 2) the enantioselective synthesis of five-membered ring natural products and unnatural derivatives.

I. ENANTIOSELECTIVE SYNTHESIS OF SIX-MEMBERED RING NATURAL PRODUCTS

Our strategy is presented in (Fig. **1**). The pivotal building block of our approaches was (+) or (−)-karahana lactone (**2**) synthesized starting from both enantiomers of 4-hydroxy-3-methylcyclohex-2-enone (**1**) prepared by enzymatic resolution of the corresponding racemic alcohol.

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Enantioselective Synthesis of Both Enantiomers of Karahana Lactone (2)

Karahana lactone (**2**) and karahana ether (**10**) are monoterpenoid with a unique 6-oxabicyclo[3.2.1]octane skeleton, which have been isolated from Japanese hop "Shinshu Wase", *Humulus lupulus L.* [1] (Fig. **2**).

Karahana ether (**10**) has already been the subject of a few racemic [2] and five enantioselective syntheses [3]. As to karahana lactone (**2**), only three syntheses have been recorded [3a,d,e]. The Mori approach [3a] proceeds from the $RuCl_3/NaIO_4$ oxidation of the corresponding karahana ether, followed by a Wittig methylenation of the keto moiety. The second approach used a biomimetic cyclization of an epoxyallylsilane [3e]. Our approach described a straightforward enantioselective synthesis of both enantiomers of karahana lactone (**2**) and karahana ether (**10**) [3d].

The starting material for the synthesis of (*R*)-(**1**) and (*S*)-(**1**) uses (±)-4-hydroxy-3-methylcyclohex-2-enone (**1**) [4]. Treatment of racemic (**1**) with vinyl acetate in the presence of *Mucor miehei* lipase (Scheme **1**) gave 59% yield of the unreacted alcohol (*S*)-(**1**) (66% ee) and 34% yield of the (*R*)-acetate (**11**) (96% ee).

The remaining alcohol was resubjected to the same conditions for enzymatic transesterification using the recovered enzyme. After 7 days, (*S*)-alcohol (**1**) was obtained in 40% overall yield (ee>99%). On the other hand, (*R*)-acetate (**11**) was hydrolyzed to afford (*R*)-alcohol (**1**) in 88% yield (96% ee; 30% overall yield from racemic (**1**)). Starting from (+)-(**1**) as an example, the synthesis of karahana lactone and the corresponding ether is described in (Scheme **2**).

Treatment of (+)-(**1**) with TBSCl gave the protected compound (+)-(**12**). This ketol was converted into the single *trans*-2-carbomethoxy-cyclohexanone (**13**) by the 1,4 addition of lithium dimethylcuprate, followed by the quenching with methylcyanoformate in HMPA [5]. Treatment of (**13**) with *p*-TsOH.H_2O afforded the crystalline keto-lactone (−)-(**14**) as a single product. The pathway can be regarded as an acid-induced domino reaction [6] in which the subsequent reaction (cyclization by transesterification) is the result of three reactions (deprotection of (**13**), epimerization and cyclization).

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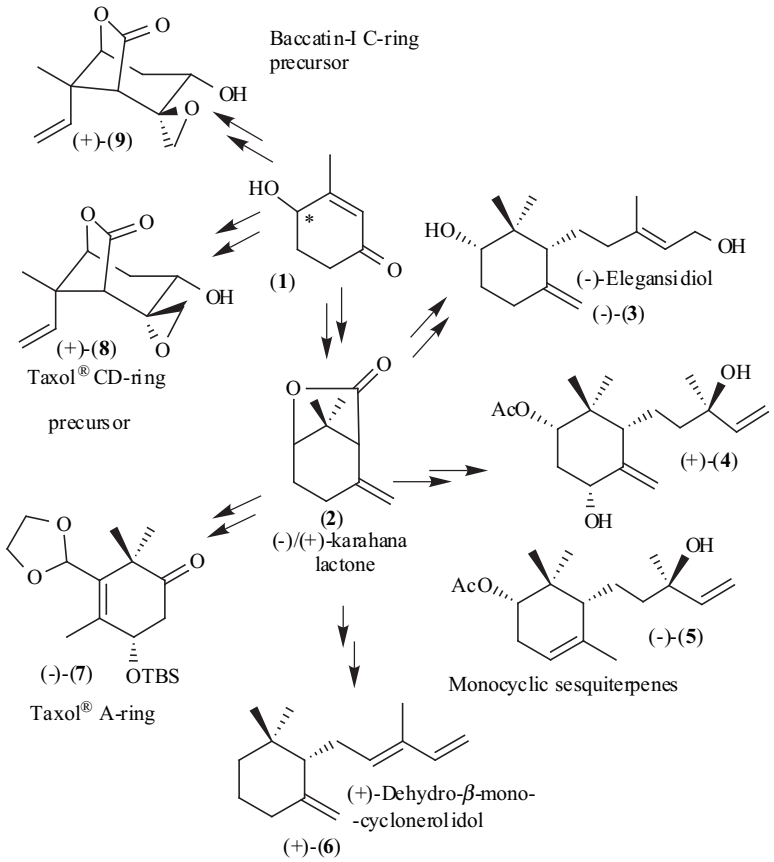


Fig. (1). Compounds synthesized starting from the optically active alcohol (**1**).

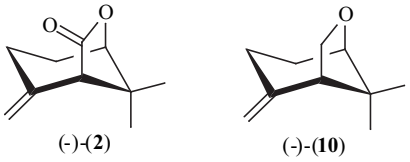
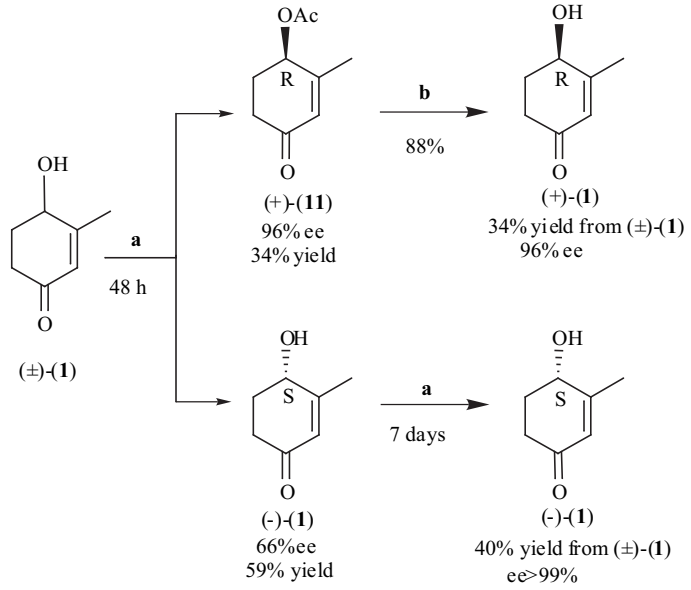
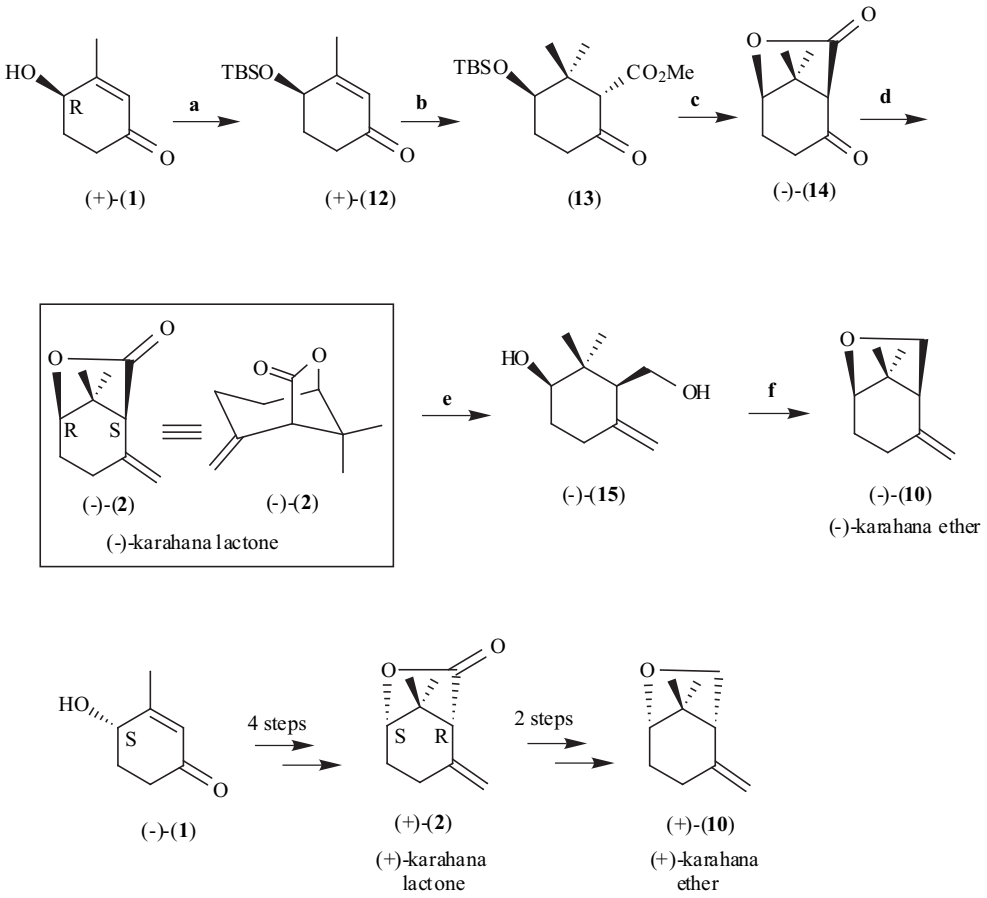


Fig. (2). Structure of (–)-karahana lactone (**2**) and (–)-karahana ether (**10**).



Reagents: (a) 3 equiv. vinyl acetate, $i\mathrm{Pr}_2\mathrm{O}$, *Mucor miehei* lipase; (b) $\mathrm{Na}_2\mathrm{CO}_3$, MeOH.

Scheme 1. Enantioselective synthesis of alcohol (+)-(**1**) and (–)-(**1**).



Reagents and conditions: (a) TBSCl, imidazole, DMF (92%); (b) 2 equiv. Me_2CuLi then HMPA and $CNCO_2Me$ (80%); (c) 1.2 equiv. *p*-TsOH.H_2O, toluene, reflux 1/2 h (94%); (d) 2.5 equiv. $Ph_3P^+CH_3,I^-$, t-BuOK, toluene, reflux 3 h (80%); (e) $LiAlH_4$, ether (95%); (f) 1 equiv. TsCl, pyr (81%).

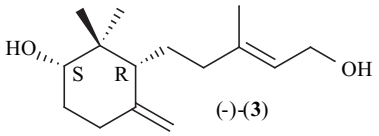
Scheme 2. Enantioselective synthesis of karahana lactone (**2**) and karahana ether (**10**).

In the final step, treatment of (–)-(**14**) with the salt-free Wittig reagent gave crystalline karahana lactone (–)-(**2**). Purification by recrystallization improved the optical purity of (–)-(**2**) (ee>99%). When karahana lactone (–)-(**2**) was treated with lithium aluminum hydride, the diol (–)-(**15**) was isolated as a single diastereomer. Reaction of (–)-(**15**) with *p*-toluenesulfonyl chloride afforded the bicyclic karahana ether (–)-(**10**). The same pathway, starting from (–)-(**1**), gave (+)-karahana lactone, (+)-(**2**), and (+)-karahana ether**,** (+)-(**10**). So, the synthesis of both enantiomers of karahana lactone has been achieved in four steps and a 63% overall yield starting from a lipase resolved ketol (**1**).

Enantioselective Synthesis of (–)-elegansidiol (–)-(3)

In 1999, Barrero *et al*. [7] isolated a new sesquiterpene, elegansidiol (–)-(**3**), from the hexane extracts of the aerial parts of *Santolina elegans.* They established the structure on the basis of its spectroscopic properties and confirmed the structural assignments *via* a racemic chemical synthesis, but the absolute configuration of (–)-elegansidiol still remained unknown (Fig. **3**).

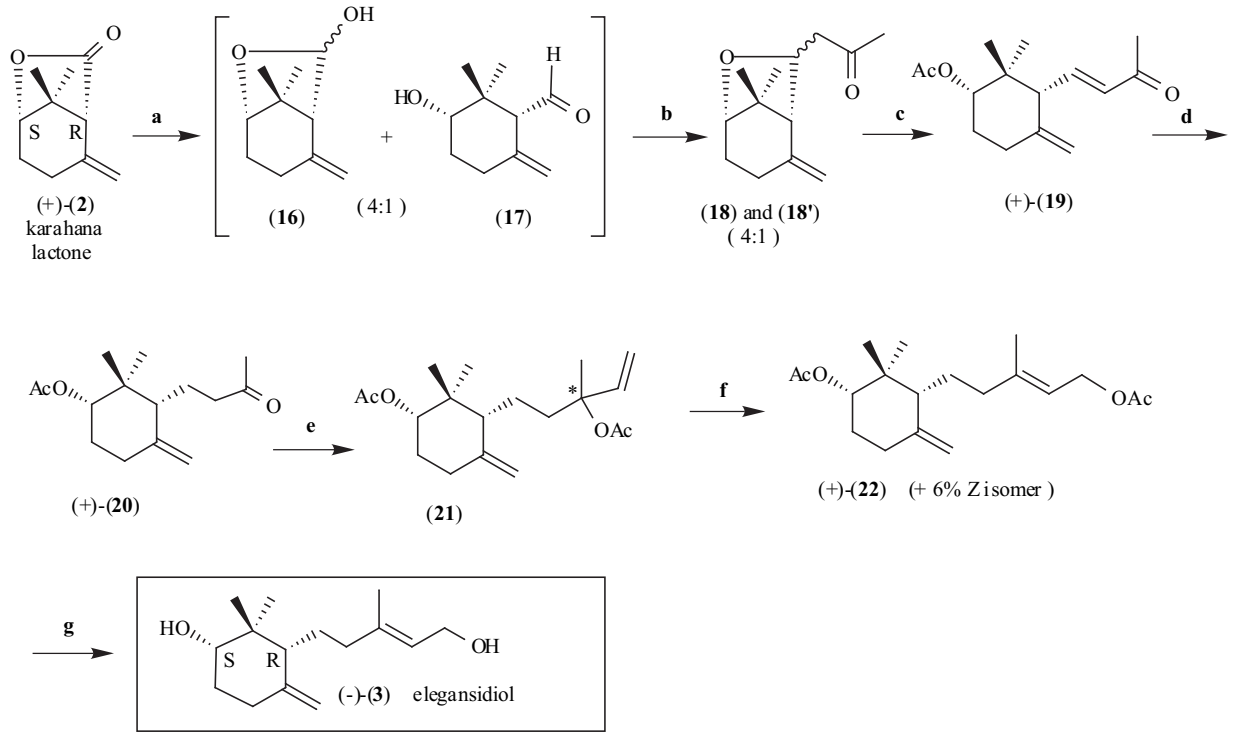
We described the first straightforward enantioselective synthesis of (–)-**3** based on an original approach [8] and starting from karahana lactone (**2**) for the introduction and determination of the absolute stereochemistry.



elegansidiol

Fig. (3). Chemical structure of elegansidiol, (–)-(**3**), is represented with the absolute stereochemistry as determined in our work.

As shown in (Scheme **3**), the reduction of (+)-(**2**) gave a mixture of diastereomeric lactols (**16**) and aldehyde (**17**) and the reaction with the barium derivative of diethyl 2-oxopropylphosphonate afforded a 4:1 mixture of ((**18**) + (**18'**)) as unique products. Acylation of this mixture produced crystalline (+)-(**19**) as a single *E*-double bond stereoisomer *via* an irreversible retro Michael addition process. The best chemoselective 1,4- conjugate reduction of the α,β-enone system of (+)-(**19**) was achieved using Bu_3SnH/palladium as catalyst in the presence of anhydrous $ZnCl_2$ as the reducing system [9] and afforded (+)-(**20**). Subsequent exposure of (+)-(**20**) to vinylmagnesium bromide and treatment of the crude alcohols with acetic anhydride/triethylamine in the presence of DMAP gave diastereomeric diacetates (**21**).



Reagents and conditions: (a) DIBAL, toluene, –70 °C, 95%; (b) $(EtO)_2P(O)CH_2COMe$, $Ba(OH)_2$, THF, room temp., 92%; (c) Ac_2O, PPTS, toluene, reflux, 81%; (d) $HSnBu_3$, $Pd(PPh_3)_4$, $ZnCl_2$, THF, room temp., 88%; (e) (i) CH_2=CHMgBr, THF, –20 °C; (ii) Ac_2O, Et_3N, DMAP, THF, reflux, 85%; (f) $Cl_2Pd(II)(MeCN)_2$, THF, room temp., 95%; (g) (i) K_2CO_3, MeOH, room temp., quant.; (ii) recrystallization from Et_2O-petroleum ether.

Scheme 3. Enantioselective synthesis of (–)-elegansidiol (–)-(**3**).

Treatment of acetates (**21**) with dichlorobis(acetonitrile) palladium (II) [10], afforded diacetate (+)-(**22**). Exposure of (+)-(**22**) to K_2CO_3 in methanol produced quantitatively elegansidiol (−)-(**3**) as a white solid (a 94:6 *E*:*Z* mixture). Recrystallization from Et_2O-petroleum ether furnished pure elegansidiol (−)-(**3**). The (1*S*,3*R*)-configuration was therefore assigned to the natural elegansidiol. The difference observed in the numerical value of the specific rotation (−14.0 versus −4.0) seems to imply that natural (−)-elegansidiol is partially racemic.

Enantioselective Synthesis of two Monocyclic Sesquiterpenes (+)-(4) and (−)-(5)

Oxygenated monocyclic terpenoids are not very common metabolites in the nature because biosynthetic processes are usually based on polycyclization. However, during the last few years, identification of several natural oxygenated monocyclic sesquiterpenes suggests that they may be more prevalent than it was presumed within the plant kingdom [11]. In 1996, Marco *et al*. [12] isolated two new monocyclic sesquiterpenes (**4**) and (**5**) from the aerial parts of *Artemisia chamaemelifolia* ssp. *Chamaemelifolia* (Fig. **4**). These authors established both the structure and relative stereochemistry of (**4**) and (**5**) by spectroscopy but the absolute configurations still remained unkown. Since then, only one racemic synthesis of (**4**) has been published [13].

Starting from karahana lactone (+)-(**2**) as the enantiopure building block for the introduction and determination of the absolute stereochemistry, we have carried out the first enantioselective synthesis of (+)-(**4**) [14] to confirm the structural assignment and to determine the absolute stereochemistry of the four chiral centers present in the natural product. Our methodology is depicted in (Scheme **4**). The allylic hydroxylation afforded the alcohol (+)-(**23**) as a single stereomer. The stereochemistry of the hydroxyl function was inverted at this stage by a two-step procedure. Dess-Martin periodinane oxidation of (+)-(**23**) and subsequent $NaBH_4$-$CeCl_3$ Luche reduction of the intermediate ketone afforded the single stereomer *epi*-(**23**). The protection of the hydroxyl group of *epi*-(**23**) was conducted on the crude alcohol and TBS derivative (+)-(**24**) was obtained. Reduction of (+)-(**24**) afforded a mixture of diastereomeric lactols (**25**). Application of HWE reaction to the mixture (**25**) gave an easily separable 1:3 mixture of the expected derivative (+)-(**26**) and diastereomeric bicyclic compounds (**27**).

Acylation of (+)-(**26**) and irreversible retro-Michael acylation of (**27**) furnished crystalline (+)-(**28**) as a single E

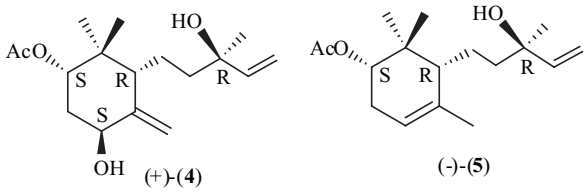


Fig. (4). Natural monocyclic sesquiterpenes (+)-(**4**) and (−)-(**5**) are represented with the absolute stereochemistry as determined in our work.

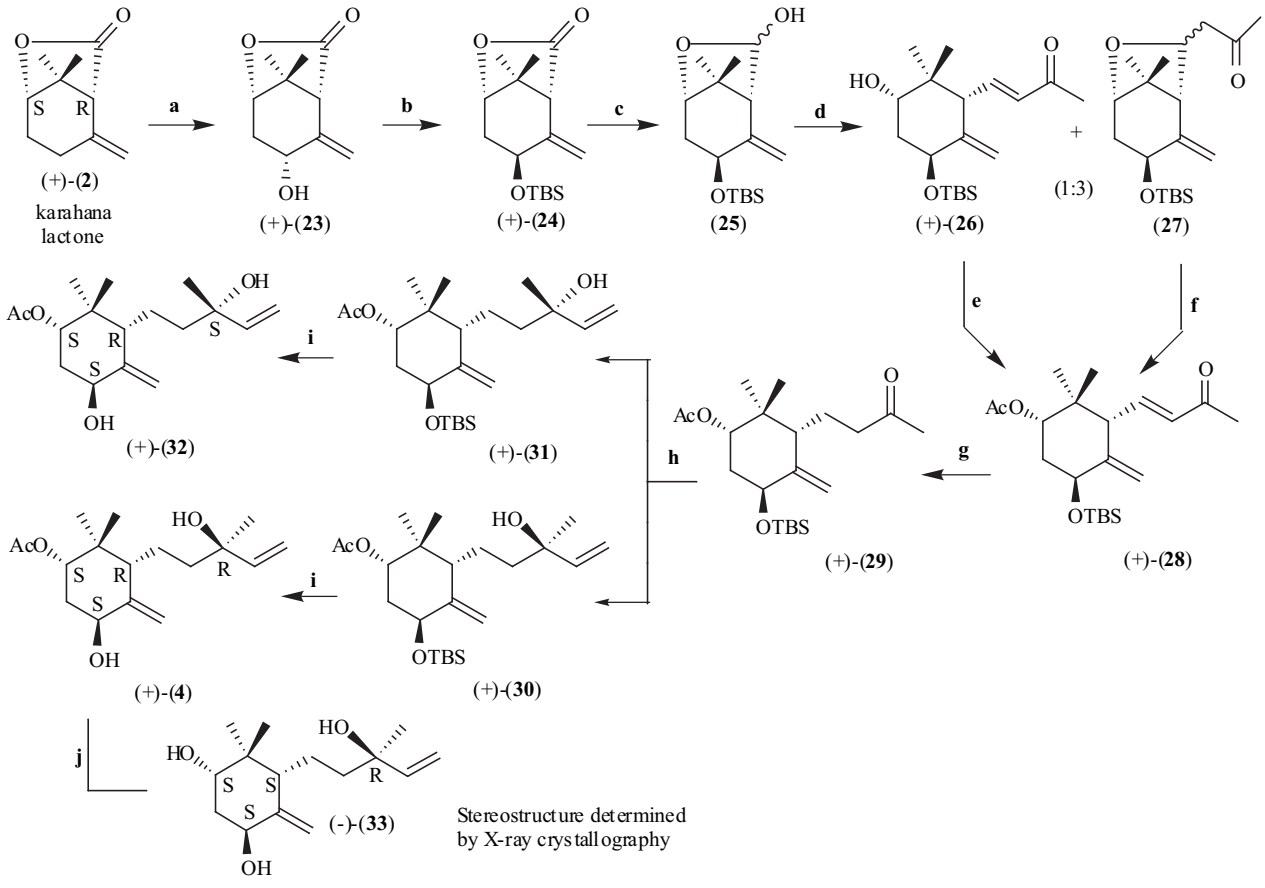
stereomer. The chemoselective 1,4-conjugate reduction of the α,β-enone system of (+)-(**28**) yielded 83% of (+)-(**29**). Subsequent exposure of (+)-(**29**) to vinylmagnesium bromide furnished the two desired diastereomeric alcohols (**30**) and (**31**) in a 2:1 ratio and 90% combined yield. Gratifyingly, (+)-(**30**) and (+)-(**31**) differ significantly in polarity and therefore proved to be chromatographically separable at this stage. Removal of the TBS protecting group of (+)-(**30**), the first eluted derivative, and (+)-(**31**) furnished the corresponding dihydroxy acetate (+)-(**4**) and (+)-(**32**), respectively. The spectroscopic data (IR, ^{1}H and ^{13}C NMR) of synthetic (+)-(**4**) matched that reported for natural **4** and the specific rotation was comparable in magnitude and the same in sign, indicating the synthesis of the natural enantiomer. The remaining task for the complete identification was the determination of the absolute stereochemistry of the quaternary stereogenic center at the side chain of (+)-(**4**). This stereochemistry was unequivocally determined to be the *R* configuration *via* reduction of (+)-(**4**) to the corresponding crystalline triol (−)-(**33**) and subsequent X-ray crystallographic analysis. Therefore, the absolute stereochemistry of the natural product was established as (+)-(**4**), depicted in (Fig. **4** and Scheme **4**).

With (+)-(**4**) in hand, our attention was then focused on the synthesis of the target molecule (−)-(**5**) from (+)-(**4**) using, as the key step, the reductive transposition of an allylic derivative (Scheme **5**).

Of the several methods available to reach our goal [15], the two-steps procedure using transformation of (+)-(**4**) into allylic mesylate and hydrogenolysis of the mesylate with $LiAlH(O^tBu)_3$ was found to be the most effective, giving the desired target (−)-(**5**) and its exocyclic double bond regioisomer in a 92:8 ratio and 70% yield (two steps). This by-product posed minimal problem as it was easily removed by careful flash chromatography to afford pure (−)-(**5**). The absolute stereochemistry of the natural product was established as (−)-(**5**), depicted in (Fig. **4** and Scheme **5**).

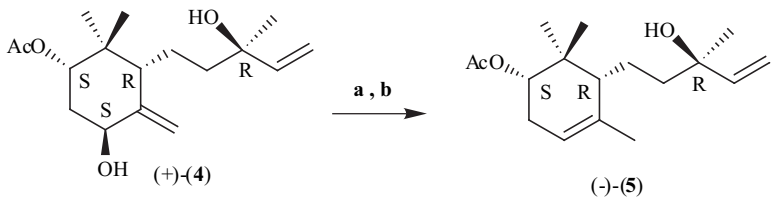
Enantioselective Synthesis of Dehydro-β-Monocyclonerolidol (+)-(6)

In 1996, Asakawa *et al.* [16] isolated the new monocyclofarnesane-type sesquiterpenoid (+)-(**6**) from the non-pungent group of liverwort *Porella subobtusa* (Fig. **5**). They characterized its structure as dehydro-β-monocyclonerolidol by extensive NMR techniques except for the absolute configuration which remained unknown.



Reagents and conditions: (a) cat. SeO_2, cat. salicylic acid, *t*-BuOOH 70 % in water, CH_2Cl_2, reflux, 85%; (b) (i) Dess-Martin reagent, CH_2Cl_2, (ii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, –18°C, 83% (two steps), (iii) TBSCl, imidazole, DMF, rt, 78%; (c) DIBAL, toluene, -78°C, 89%; (d) $(EtO)_2P(O)CH_2COMe$, $Ba(OH)_2$, THF, rt, 92%; (e) Ac_2O, Pyr, rt, 91%; (f) Ac_2O, PPTS, toluene, reflux, 89%; (g) $HSnBu_3$, cat. $Pd(PPh_3)_4$, $ZnCl_2$, THF, rt,83%; (h) CH_2=CHMgBr, THF, – 20°C, then separation by Flash chromatography; (i) TBAF, THF, rt, 95%; (j) $LiAlH_4$, ether, rt, 99%.

Scheme 4. Enantioselective synthesis and determination of the absolute configuration of the monocyclic sesquiterpene (+)-(**4**).



Reagents and conditions: (a) MsCl, CH_2Cl_2-Pyr. (1:1), rt, (b) 5 equiv. $LiAlH(OtBu)_3$, Et_2O, rt, 70% (two steps).

Scheme 5. Enantioselective synthesis and determination of the absolute configuration of the monocyclic sesquiterpene (−)-(**5**).

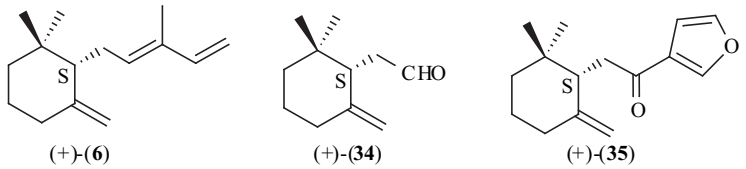
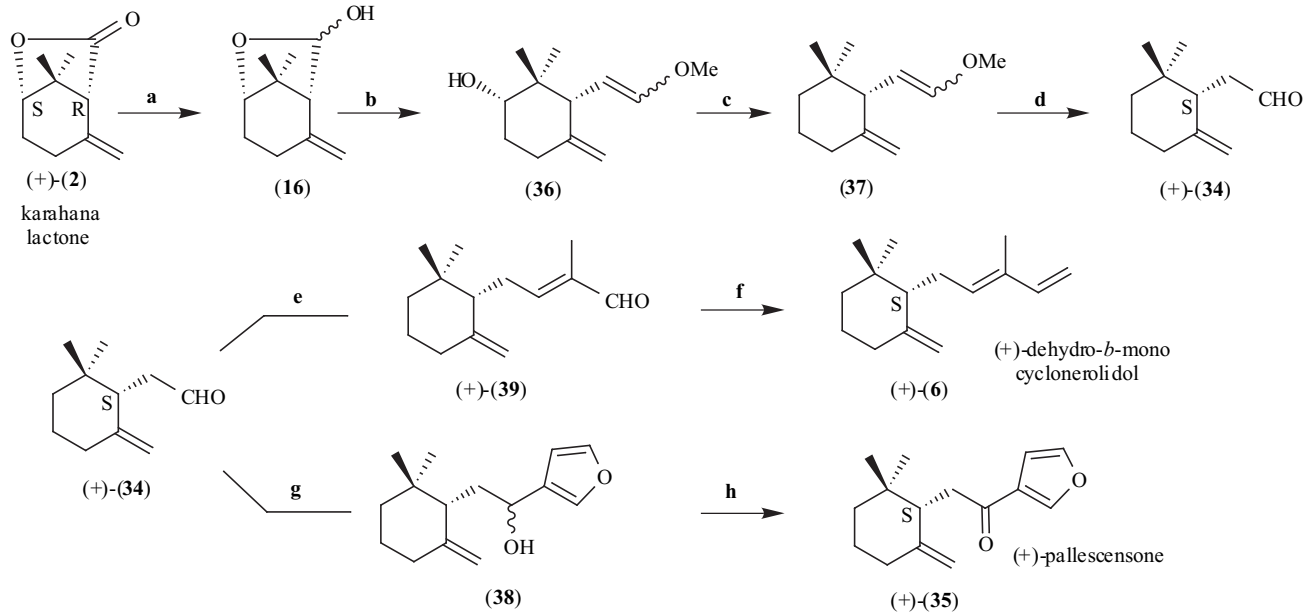


Fig. (5). Natural (+)-dehydro-β-monocyclonerolidol (+)-(**6**) is represented with the absolute stereochemistry as determined in our work.

Like previously, our enantioselective synthesis of (+)-(**6**) was reported starting from karahana lactone for the introduction and determination of the absolute stereochemistry [17]. The used methodology also allowed the synthesis of the known γ-cyclohomocitral (+)-(**34**), as a key intermediate for the target molecule (+)-(**6**), and natural pallescensone (+)-(**35**) [18] [19]. Our synthetic plan is outlined in (Scheme **6**). Reduction of (+)-(**2**) as previously described, gave a mixture of diastereomeric lactols (**16**) and exposure of the crude products mixture (**16**) to the α-methoxy substituted ylid afforded (**36**) as a mixture of stereoisomers. Barton-McCombie deoxygenation of (**36**) provided (**37**) in an overall yield of 90% and subsequent hydrolysis gave γ-cyclohomocitral (+)-(**34**). The chiral information was encoded in this key intermediate whose the absolute configuration is (*S*). The aldehyde (*S*)-(**34**) was subjected to Wittig olefination to form stereoselectively the chain extended *E*-α,β-unsaturated aldehyde (+)-(**39**) as a single stereoisomer. Finally, subsequent methylenation of (+)-(**39**) furnished the target molecule (+)-(**6**).

The specific rotation of (**6**) was comparable in magnitude and the same in sign, $[\alpha]_D^{25}$+10.3 ($CHCl_3$) / lit. $[\alpha]_D^{20}$ +9.5 ($CDCl_3$), indicating the synthesis of the natural enantiomer. The (*S*)-configuration was therefore assigned to natural dehydro-β-monocyclonerolidol (+)-(**6**). Additionally, (+)-γ-cyclohomocitral, (*S*)-(**34**), was converted into (+)-pallescensone, (*S*)-(**35**), in two steps according to published procedures [20].



Reagents and conditions. (a) DIBAL, toluene, – 70°C, 95%; (b) $Ph_3P^+CH_2OMeCl^-$, n-BuLi, THF, rt, 82%; (c) i. NaH, CS_2, MeI, rt, THF; ii. $HSnBu_3$, cat. AIBN, toluene, reflux, 90% (two steps); (d) 1M HCl / THF : 1 / 2, rt, THF, 79%; (e) $Ph_3P{=}C(CH_3)CHO$, toluene, reflux, 90%; (f) $Ph_3P^+MeI^-$, t-BuOK, toluene, rt, 92%; (g) 3-bromofuran, n-BuLi, THF, −78°C, 80%; (h) NMO, cat. $(n\text{-}Pr)_4NRuO_4$, 4Å MS, CH_2Cl_2, rt, 70%.

Scheme 6. Enantioselective synthesis of dehydro-β-monocyclonerolidol (+)-(**6**) and pallescensone (+)-(**35**).

Enantioselective Taxanes Approach Using Both Enantiomers of the Same Building-Block

Taxol® (Fig. **6**) and its analogs are well-known to exhibit promising antitumor activity and several other natural taxanes were recently revealed to be inhibitors against the P-glycoprotein [21,22]. These properties have stimulated considerable effort towards a wide variety of strategies for construction of the core structure.

To date, six total syntheses of paclitaxel [23] have been reported and two of them, the Nicolaou [23a] and Danishefsky [23b] routes, utilized a A + C rings connection to form the central B-ring. In spite of these successes, convenient accesses to the fully functionalized A-ring, C-ring and the construction of the sterically congested eight-membered B-ring remain a challenge and excellent works are still in progress [24]. In the course of our interest in the synthesis of natural products, we investigated syntheses for the taxoid diterpene framework precursors.

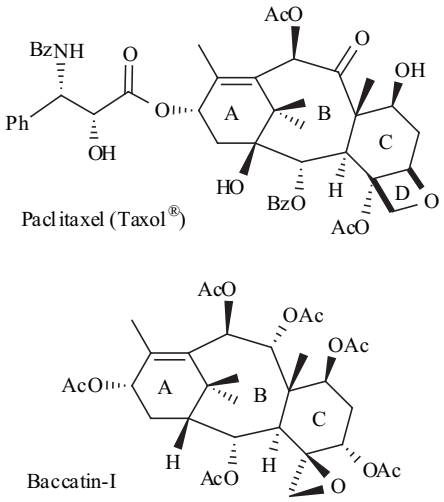


Fig. (6). Structure of Paclitaxel and Baccatin-I.

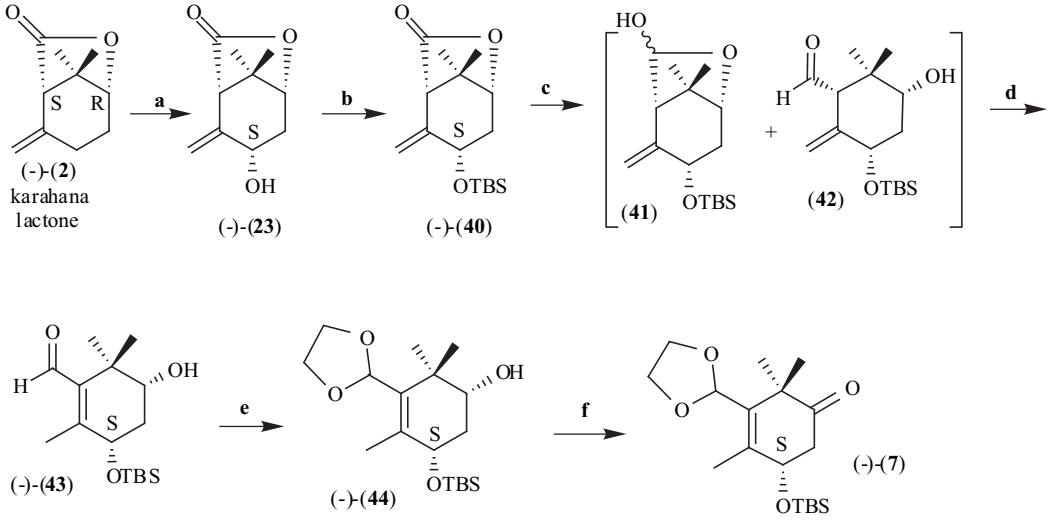
Synthesis of A-Ring of Taxanes

In 2002, we described an enantioselective synthesis of fully-oxygenated Taxol® A-ring (**7**) [25] using (1*S*,5*R*)-karahana lactone, (–)-(**2**), as an enantiopure starting building block and a diastereoselective allylic hydroxylation as the key step (Scheme **7**). Allylic hydroxylation of (–)-(**2**) afforded the alcohol (–)-(**23**) as a single stereomer. Treatment of (–)-(**23**) with TBSCl gave the protected derivative (–)-(**40**). Reduction of (–)-(**40**) with DIBAL provided a mixture of lactols (**41**) and aldehyde (**42**). The crude products mixture was subjected to isomerization to α,β-unsaturated aldehyde in the presence of catalytic MeONa/MeOH to afford (–)-(**43**) in 90% yield. Reaction of (–)-(**43**) with ethane-1,2-diol afforded dioxolane (–)-(**44**) without migration of the double bond to the exocyclic β,γ-position. Finally, Dess-Martin periodinane oxidation of (–)-(**44**) gave the desired target (–)-(**7**).

Synthesis of C-ring of Taxanes

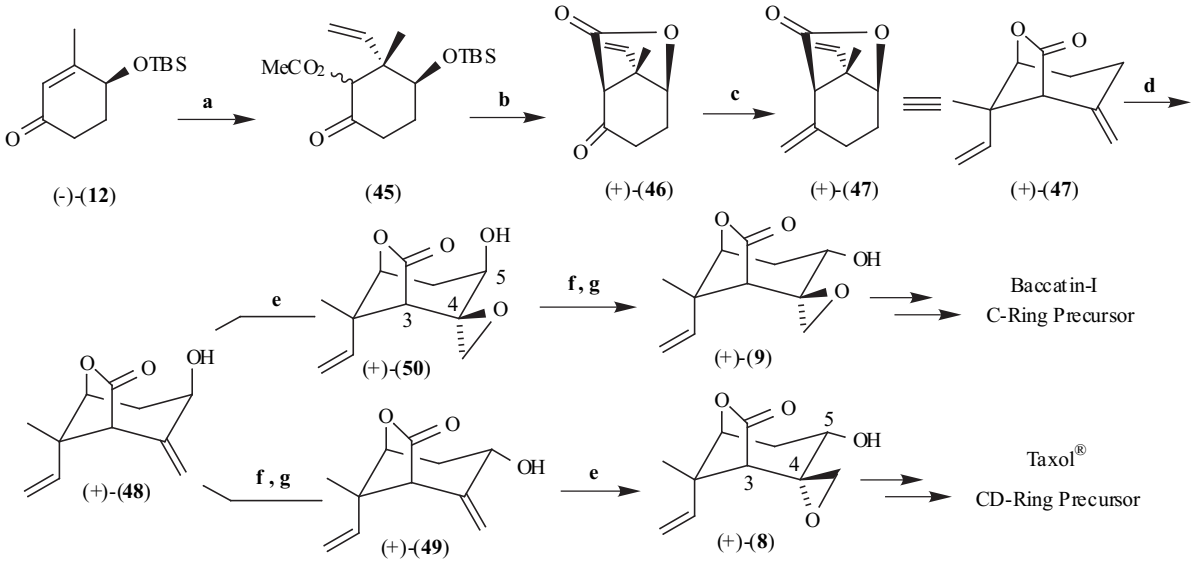
We also reported a stereocontrolled approach toward highly oxygenated taxane C and CD-ring precursors (+)-(**8**) and (+)-(**9**) [26]. Our methodology is outlined in (Scheme **8**).

The starting material is the protected derivative (–)-(**12**) which was converted to 2-carbomethoxycyclohexanone (**45**) by copper-catalyzed 1,4-addition of vinylmagnesium bromide followed by the quenching with methylcyanoformate. Treatment of (**45**) with *p*-TsOH.H_2O afforded the keto-lactone (+)-(**46**) and reaction with the salt-free Wittig reagent gave lactone (+)-(**47**). Allylic hydroxylation of (+)-(**47**) provided alcohol (+)-(**48**) as a single stereomer in 85% isolated yield. Subjection of (+)-(**48**) to hydroxyl directed epoxidation, ($VO(acac)_2$, *t*-BuOOH), gave an 88% isolated yield of the epoxy-alcohol (+)-(**50**). The stereochemistry of C-5 was inverted at this stage by a two-step procedure using Dess-Martin periodinane oxidation and subsequent $NaBH_4$-$CeCl_3$ Luche reduction. This sequence afforded the C-5α hydroxylated Baccatin-I C-



Reagents and conditions: (a) Cat. SeO_2, cat. salicylic acid, *tert*-BuOOH 70 % in water, CH_2Cl_2, reflux, 85%. (b) TBSCl, imidazole, DMF, rt, 72%. (c) DIBAL, toluene, -80°C and (d) cat. MeONa, MeOH, rt, 90%. (e) Ethane-1,2-diol, PPTS, benzene, reflux, 71%. (f) Dess-Martin reagent, CH_2Cl_2, rt, 86%.

Scheme 7. Enantioselective synthesis of A-ring of taxanes (–)-(**7**).



Reagents and conditions: (a) CH_2=CHMgBr, CuBr.SMe_2, THF, – 78°C, then HMPA and $CNCO_2Me$, – 78°C to rt, 81%; (b) 1.2 equiv. *p*-TsOH.H_2O, toluene, reflux, 92%; (c) 2.5 equiv. $Ph_3(CH_3)P^+I^-$, *t*-BuOK, toluene, rt, 83 %; (d) cat. SeO_2, cat. salicylic acid, *t*-BuOOH 70 % in water, CH_2Cl_2, reflux, 85%; (e) $VO(acac)_2$, *t*-BuOOH, benzene, reflux, (+)-(**50**) 88%, (+)-(**8**) 74%; (f) Dess-Martin reagent, CH_2Cl_2 and (g) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, –18°C, (+)-(**9**) 89%, (+)-(**49**) 85%.

Scheme 8. Enantioselective synthesis of Taxol® CD-ring precursor (+)-(**8**) and Baccatin-I C-ring precursor (+)-(**9**).

ring precursor (+)-(**9**) as a single stereomer in 89% isolated yield over two steps.

Next, for the synthesis of Taxol® CD-ring precursor (+)-(**8**), the C-4(20)-α epoxide was required. For this purpose, starting from (+)-(**48**), the same oxidation/reduction sequences clearly provided the reverse C-5α hydroxy derivative (+)-(**49**), again as a single stereomer. Hydroxyl directed epoxidation of the latter, using $VO(acac)_2$ and *t*-BuOOH led exclusively to (+)-(**8**) with the required α-epoxide stereochemistry.

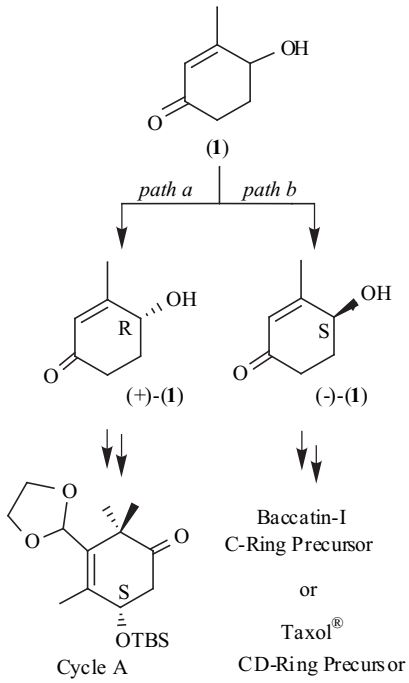


Fig. (7). Methodology using both enantiomers of the same building block (**1**).

In conclusion, as part of a program aimed at the enantioselective synthesis of taxanes using both enantiomers of the same building block, we have developed a new approach to a fully-oxygenated taxanes A-ring subunit. Starting from the opposite enantiomer, we have developed a stereoselective construction of bicyclic systems with the appropriate stereochemical disposition of the substituents belonging either to a Baccatin-I C-ring precursor or a Taxol® CD-ring precursor (Fig. **7**).

II. ENANTIOSELECTIVE SYNTHESIS OF FIVE-MEMBERED RING NATURAL PRODUCTS AND UNNATURAL DERIVATIVES

Starting from a functionalized five-membered ring (**51**) and using a lipase-promoted kinetic resolution as a crucial step, the enantioselective syntheses of natural products such as laurene (+)-(**52**), β-necrodol (–)-(**53**), lancifolol (–)-(**54**), unnatural carbasugars (**55**) and tochuinyl acetate (–)-(**56**) are presented in (Fig. **8**).

Enantioselective Synthesis of Laurene (+)-(52)

The sesquiterpene hydrocarbon laurene (Fig. **9**) was first isolated as the (+)-enantiomer (**52**) from *Laurencia glandulifera* and subsequently found in several other Laurencia species [27]. Despite the relatively simple substitution pattern on the cyclopentane skeleton, the *cis*-1,2 relationship of the secondary methyl group with the *p*-tolyl group has made both the stereoselective [28] and enantioselective [29] synthesis of this product difficult.

In 1999, we reported the first enantioselective synthesis of both enantiomers of laurene [30]. Our approach was based upon the stereoselective H-ene reaction between an isocyclic allyltrimethylsilane and paraformaldehyde, followed by an

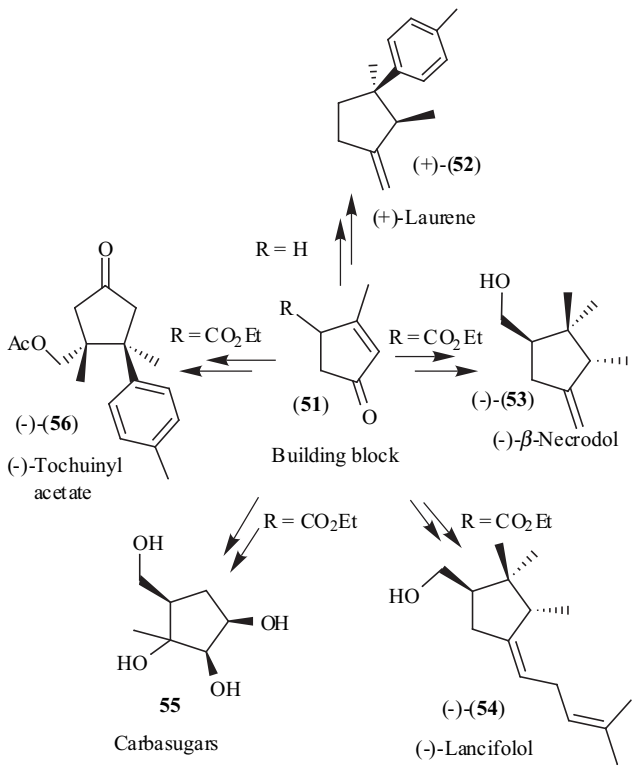


Fig. (8). Compounds synthesized from the five membered ring building block (**51**).

enzymatic kinetic resolution of the key racemate. Our methodology is described in (Scheme **9**).

The commercially available 3-methylcyclopent-2-en-1-one was converted into the cyclic diethyl enol phosphate (**57**). The $Ni(acac)_2$-catalyzed reaction of (**57**) with (trimethylsilyl) methylmagnesium chloride gave allylsilane (**58**) in 91% yield. The Me_2AlCl-induced H-ene reaction of (**58**) with paraformaldehyde furnished a mixture of three main products ((**59**) + (**60**) + (**61**)) and small amounts (10%) of a fourth (**62**). Compounds (**59**), (**60**) and (**61**) had the carbon stereostructure of laurene and (**62**) that of *epi*-laurene. Remarkably, treatment of the mixture ((**59**) + (**60**)) with HCl in MeOH provided the alcohol (**61**) as the only product in 78% overall yield based on (**58**).

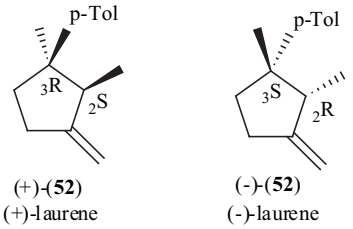
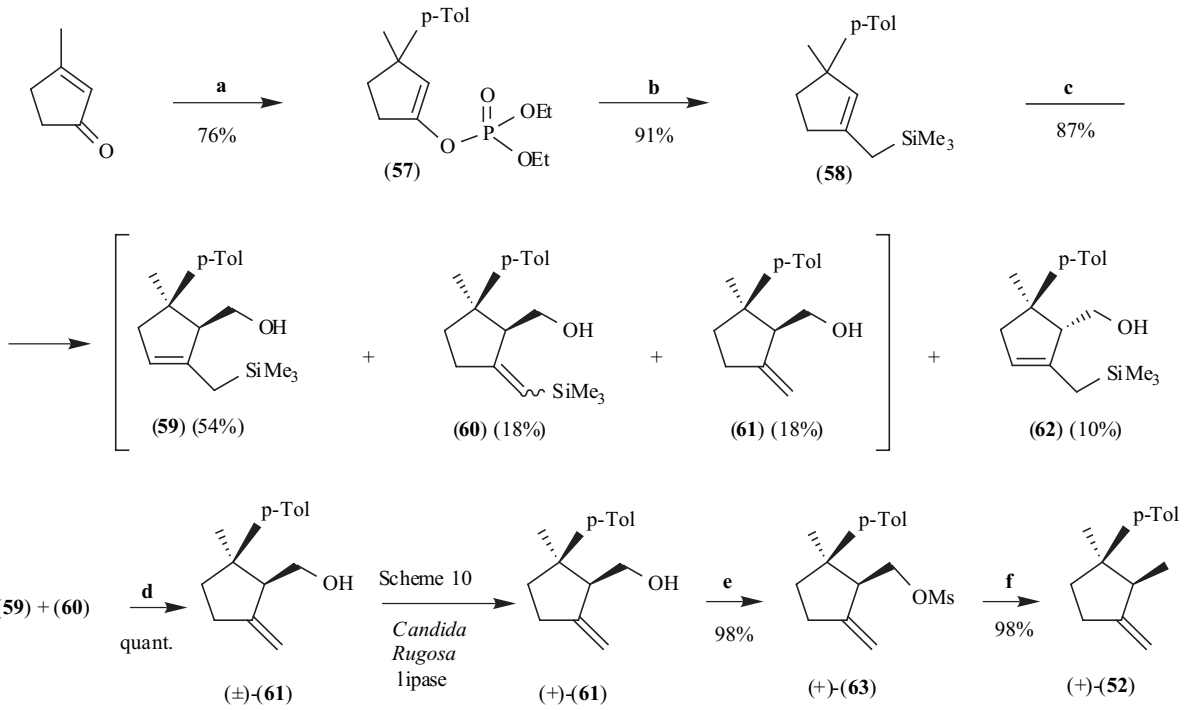


Fig. (9). Structure of (+)-laurene, (+)-(**52**), and (–)-laurene, (–)-(**52**).

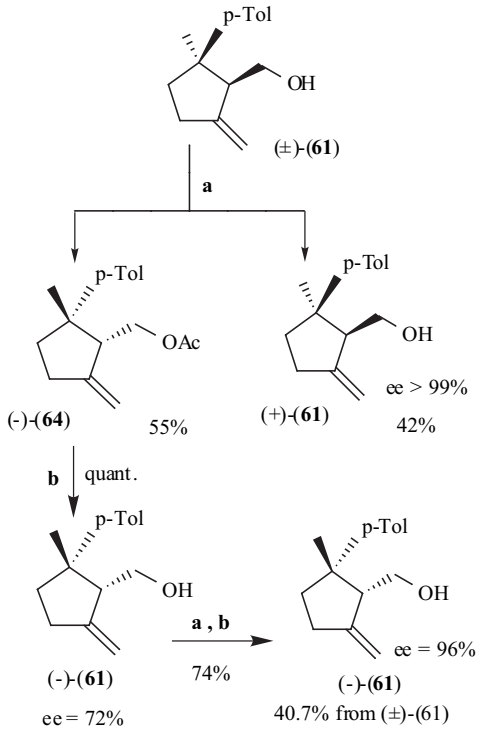
Treatment of (**61**) with vinyl acetate in the presence of *Candida rugosa* lipase gave 42% of unreacted alcohol (+)-(**61**) (ee > 99%) and 55% of acetate (–)-(**64**) (Scheme **10**). Acetate (–)-(**64**) was hydrolysed and the resulting alcohol, (–)-**61** (ee 72%) was resubjected to enzymatic transesterification to provide, after a new hydrolysis, 74% of alcohol (–)-(**61**) (ee >96%).

The overall production of (+)-(**61**) and (–)-(**61**) from racemic (**61**) was 42% and 41% respectively. Treatment of alcohol (+)-(**61**) with an excess of MsCl in pyridine afforded



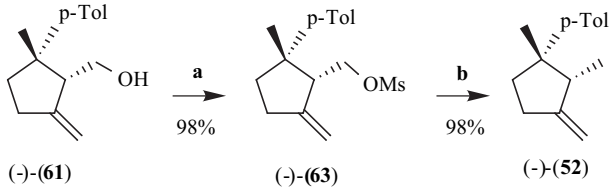
Reagents and conditions: a) *p*-TolylMgBr, CuBr.SMe_2 then $ClPO(OEt)_2$, HMPA; b) $ClMgCH_2SiMe_3$, $Ni(acac)_2$; c) $(CH_2O)_n$, Me_2AlCl, MS 4Å, CH_2Cl_2; d) MeOH, HCl; e) MsCl, Py; f) $LiAlH_4$.

Scheme 9. Enantioselective synthesis of laurene (+)-(**52**).



Reagents: (a) Vinyl acetate, lipase CRL; (b) KOH, MeOH.

Scheme 10. Enantioselective synthesis of alcohol (+)-(**61**) and (–)-(**61**).



Reagents and conditions: a) MsCl, Py; b) $LiAlH_4$.

Scheme 11. Enantioselective synthesis of laurene (–)-(**52**).

the corresponding mesylate (+)-(**63**), which was then reduced with $LiAlH_4$ in refluxing Et_2O to (+)-laurene (**52**). The same sequence applied to alcohol (–)-(**61**) provided unnatural (–)-laurene (Scheme **11**).

Enantioselective Synthesis of β-Necrodol (–)-(53)

The beetle family Silphidae comprises species of considerable ecological significance that are mostly carrion feeders. Discovered [31] in the defence spray of *necrodes surinamensis*, the so-called red-lined carrion beetle, (–)-(1*R*,3*R*)-β-necrodol (–)-(**53**) and its α-isomer ((–)-α-necrodol)

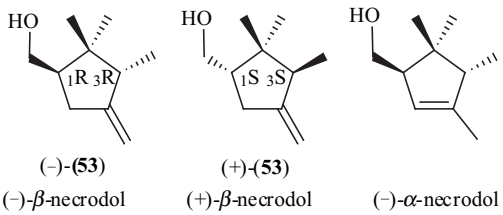


Fig. (10). Structure of (–)-β-necrodol (–)-(**53**), (+)-β-necrodol, (+)-(**53**), and (–)-α-necrodol.

constitute members of a new class of monoterpenes possessing the non-isoprenoid 1,2,2,3,4-pentamethylcyclopentane skeleton (Fig. **10**).

Because of their fascinating structures and insect repellant activity, these compounds continue to be targets of synthetic investigations [32]. The synthetic challenge represented by the necrodanes involves the construction of the sterically hindered cyclopentane core with total control of the thermodynamically unfavorable trans 1,3-stereochemistry. Until now, total diastereoselection had not been achieved with mixtures of *trans*- and *cis*-necrodane structures being obtained. We reported an enantioselective synthesis of natural (–)-β-necrodol and its enantiomer in which the complete 1,3-diastereoselection has been achieved and which is based upon an efficient lipase-assisted kinetic resolution [33].

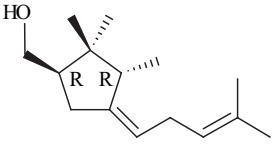
Ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate [34] was converted into the keto ester (±)-(**65**) by the $Ni(acac)_2$-catalyzed 1,4-addition of dimethylzinc, followed by quenching with methyl iodide in HMPA (Scheme **12**). Reduction of (±)-(**65**) proceeded with high stereoselectivity (30:1) to give *cis* alcohol (±)-(**66**). Treatment of racemic (**66**) with vinyl acetate in the presence of *Pseudomonas* sp lipase (Amano AK lipase) gave a 44% yield of the acetate (–)-(**68**) (Scheme **13**). Acetate (–)-(**68**) was hydrolyzed with K_2CO_3/MeOH to afford alcohol (+)-(**66**) in 93% yield (> 98% ee, 41% overall yield from racemic (**66**)).

The remaining alcohol (–)-(**66**) was resubjected in the same conditions to enzymatic transesterification and after 24 h, (–)-(**66**) was obtained in 45% overall yield and > 98% ee. In order to confirm the relative configurations of substituents in compounds (±)-(**65**) and (±)-(**66**), the absolute configuration of alcohol (+)-(**66**) was determined. Thus, the crystalline ester (–)-(**69**) was synthesized and submitted to X-ray crystallography.

Swern oxidation of (–)-(**66**) afforded the ketoester (+)-(**65**) and the keto group of (+)-(**65**) was methylenated [35] in THF to give (–)-(**67**) in 88% yield. Finally, reduction of (–)-(**67**) furnished the natural (–)-(1*R*,3*R*)-β-necrodol, (–)-(**53**) in 98% yield and > 98% ee. Starting from alcohol (+)-(**66**), this synthetic pathway formally constitutes a total synthesis of non-natural (+)-(1*S*,3*S*)-β-necrodol, (+)-(**53**).

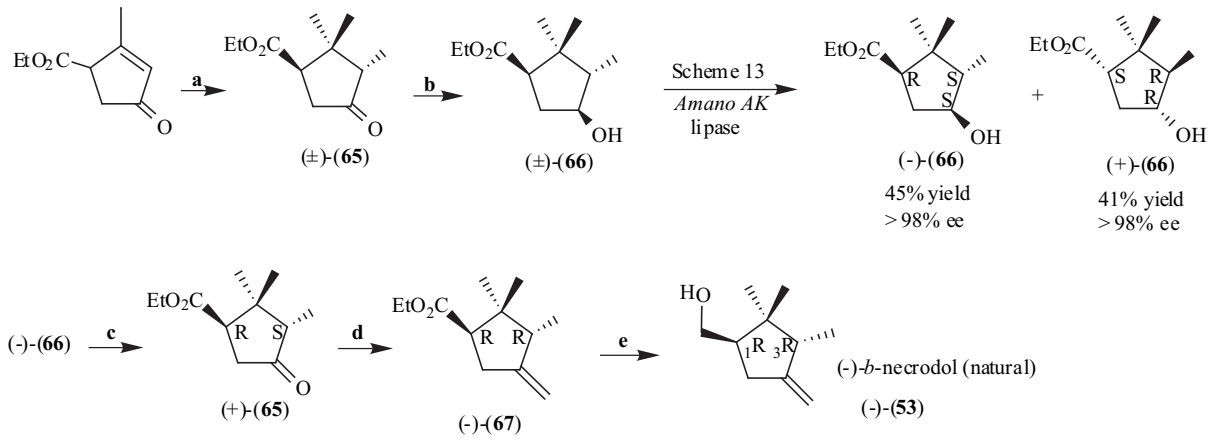
Enantioselective Synthesis of Lancifolol (–)-(54)

Lancifolol (**54**) is an irregular sesquiterpene alcohol (Fig. **11**) extracted from roots of *Peucedanum palustre* (L.) Moench (Apiaceae) and *Peucedanum lancifolium* Lange (Apiaceae) [36]. This perennial umbellifer grows at wet places, such as swampy meadows, peat bogs, alder forests, and banks of lakes in most parts of Europe extending eastwards of Central Asia. The root, named Radix Peucedani



(-)-*Z*-(**54**) lancifolol

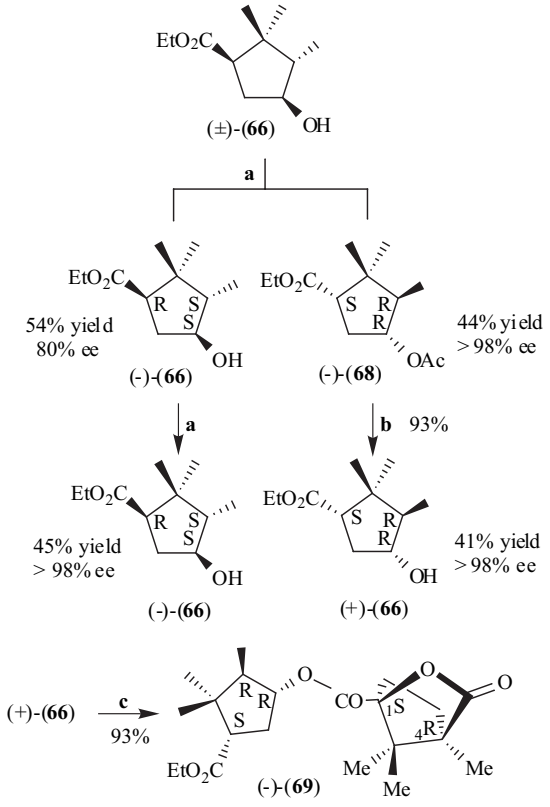
Fig. (11). Structure of lancifolol, (–)-(**54**).



Reagents and conditions: (a) Me_2Zn, $Ni(acac)_2$, THF then MeI (77%); (b) $NaBH_4$, EtOH (92%); (c) DMSO, $(ClCO)_2$, NEt_3, CH_2Cl_2 (94%); (d) $TiCl_4$-CH_2Br_2-Zn, THF, CH_2Cl_2 (88%); (e) $LiAlH_4$, Et_2O (98%).

Scheme 12. Enantioselective synthesis of β-necrodol (–)-(**53**).

palustris, was employed in folk medicine as a remedy against pertussis and spasms [37]. In Slavic countries this root served also as a substitute for ginger, probably because of its pungent and bitter taste [38].



Reagents and conditions: (a) Vinyl acetate, lipase Amano AK; (b) K_2CO_3, EtOH; (c) (–)-(1*S*,4*R*)-camphanic acid chloride, DMAP, Py.

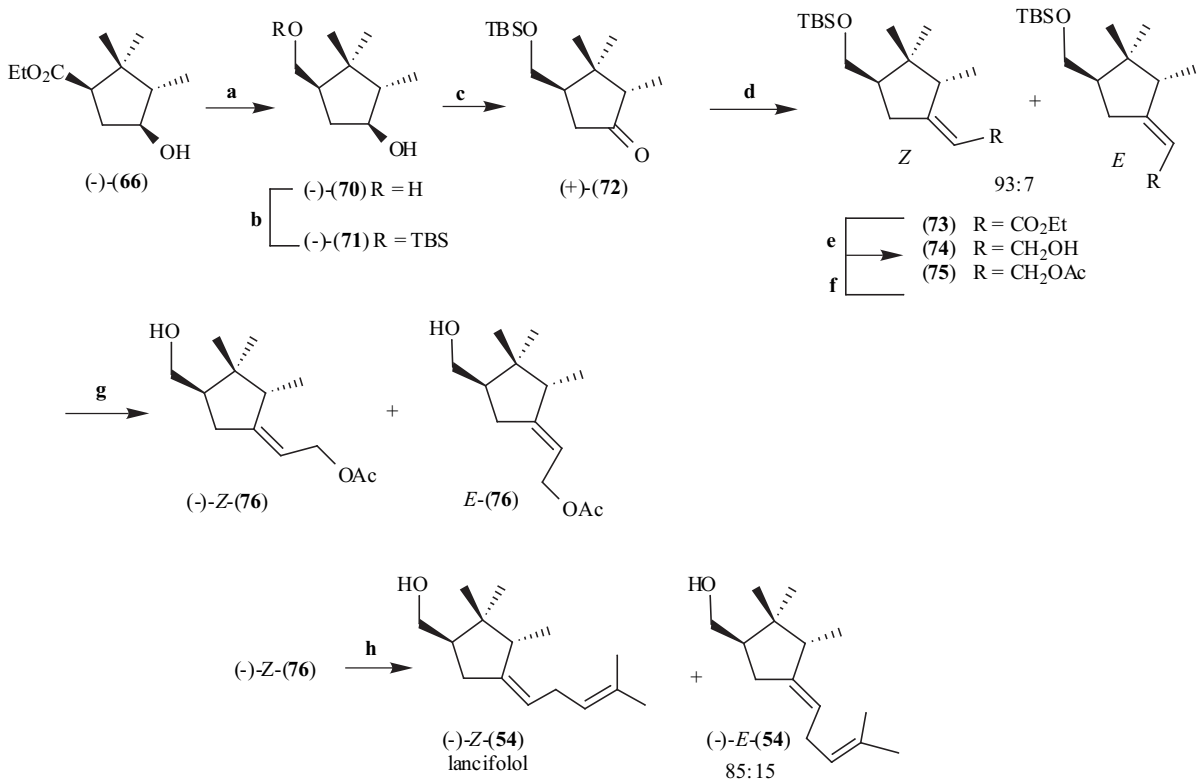
Scheme 13. Enantioselective of alcohol (+)-(**66**), alcohol (–)-(**66**) and ester (–)-(**69**).

Structure elucidations of lancifolol (**54**) was carried out mainly by homo-and heteronuclear correlated NMR-spectroscopy but, up to now, no synthesis of this product has been reported. We reported the first enantioselective synthesis of both enantiomers of lancifolol [39]. This approach allowed to correlate the relationship between absolute configuration and specific rotation. (1*R*,3*R*)-lancifolol, (–)-(**54**), has been synthesized employing the Peterson olefination as the crucial step in the synthesis and the final step of our strategy was the palladium-catalyzed cross-coupling reaction of organotin reagents and allylic acetate.

According to the synthetic plan (Scheme **14**), the starting point of the synthesis was ethyl-(*1R*, *3S*, *4S*)-4-hydroxy-2,2,3-trimethylcyclopentane carboxylate (–)-(**66**) previously prepared in enantiomerically pure form in the enantioselective synthesis of β-necrodol [33]. Chemoselective protection of the primary hydroxyl group of the corresponding diol (–)-(**70**) provided the desired cyclopentanol (–)-(**71**) and oxidation of (–)-(**71**) gave (+)-(**72**). With (+)-(**72**) in hand, we turned our attention to the major problem of the synthesis which was the *Z*-stereocontrolled olefination. Treatment of (+)-(**72**) in THF with 2 equiv. of ethyl lithiotrimethylsilylacetate [40] gave the α,β-unsaturated carboxylic esters (**73**) in a good chemical yield and a 93:7 *Z*/*E* ratio diastereoselectivity. Reduction of the ester moiety followed by acetylation of the resulting alcohols (**74**) gave the acetates (**75**). Removal of the TBS protecting group from acetate (**75**) furnished the corresponding derivatives *Z*-(**76**) and *E*-(**76**). Finally, the reaction of *Z*-(**76**) and isobutenyltrimethyltin proceeded smoothly and afforded isolated compounds *Z*-(**54**) (lancifolol) and *E*-(**54**) in a 85:15 molar ratio, respectively. Fortunately, we were able to readily separate these two diastereomers by column chromatography and obtained pure (–)-lancifolol, for which the specific rotation was comparable in magnitude and the same in sign, indicating the synthesis of the natural enantiomer. The same sequence applied to alcohol (+)-(**66**) provided unnatural (+)-lancifolol.

Enantioselective Synthesis of Carbasugars (77)-(81)

Polyoxygenated cyclopentanes are referred to as carbasugars, since they may be viewed as furanose mimics in which the ring oxygen has been replaced by a methylene group [41]. The lack of the typical glycosidic bond rendered



Reagents and conditions: (a) $LiAlH_4$, Et_2O, –15°C, 99%; (b) TBSCl, imidazole, DMF, -30°C, 80%; (c) cat. TPAP, NMO, 4Å MS, CH_2Cl_2, rt, 95%; (d) $Me_3SiCH_2CO_2Et$, $(C_6H_{11})NLi$, THF, –78°C 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. LiCl, $Pd(dba)_2$, 0.5% H_2O-DMF, 80°C, 61%.

Scheme 14. Enantioselective synthesis of lancifolol (–)-(**54**).

them chemically and enzymatically more stable as compared to the natural sugar derivatives [42] and rendered them biologically resistant [43]. Accordingly, their synthesis has been intensely investigated and, besides the modification of carbohydrates [44], one of the most widely used synthetic procedures for the preparation of optically active carbocyclic sugars is modification of achiral or racemic starting materials

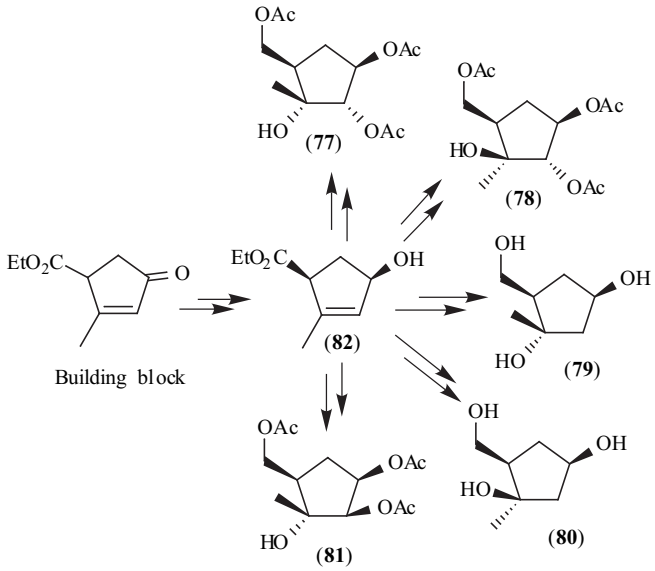


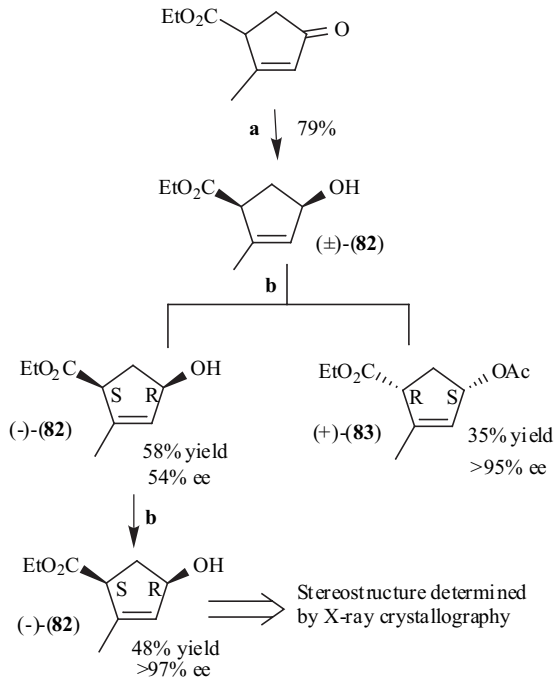
Fig. (12). 3-methylcarbapentofuranose derivatives (**77**)-(**81**) starting from a cyclopentenylcarboxylate (**82**).

[45]. Particularly, the application of lipase-catalyzed kinetic resolutions or asymmetrizations of suitable building-blocks has received increasing attention [46]. In addition to the type and further substitutions of the bases [47], the most relevant modifications which increase the antitumoral and antiviral properties are related to the nature and number of substituents of the carbapentofuranose subunit, and intense synthetic researches are still in progress [48].

We described a straightforward enantioselective approach for the preparation of optically active 3-methylcarbapentofuranose derivatives (**77**)-(**81**) [49] using a cyclopentenyl carboxylate (**82**) as the carbon building-block (Fig. **12**). All of the stereogenic centers in (**77**)-(**81**) are directed by the two stereogenic centers created in the cyclopentene moiety by an enzymatic resolution.

Ethyl 2-methyl-4-oxocyclopent-2-en-1-carboxylate was converted into the hydroxy ester (±)-(**82**) (Scheme **15**) by the Luche reduction with $NaBH_4/CeCl_3.7H_2O$ in methanol. Treatment of (±)-(**82**) with vinyl acetate in the presence of Porcine Pancreas lipase (PPL, Fluka) gave 58% of the nonreactive alcohol (1*S*,4*R*)-(**82**) (54% ee) and 35% yield of the (1*R*,4*S*)-acetate (**83**) (>95% ee). The remaining alcohol was resubjected in the same conditions to enzymatic transesterification using the recovered enzyme. After 5 days, (1*S*,4*R*)-alcohol (–)-(**82**) was obtained in 48% overall yield (>97% ee).

The absolute configuration of this alcohol was established by X-ray crystallography (Scheme **16**). Reaction



Reagents and conditions: (a) $NaBH_4$, $CeCl_3.7H_2O$. (b) Vinyl acetate, lipase PPL.

Scheme 15. Enantioselective synthesis and Lipase-catalyzed kinetic resolution of racemic (±)-(**82**).

of alcohol (–)-(**82**) with (1*S*,4*R*)-camphanic chloride afforded the derivative (**84**), but as a syrupy liquid that we were unable to crystallize despite numerous attempts. Epoxidation of the double bond of (**84**) overcame this difficulty. Thus, exposure of (**84**) to dimethyldioxirane (DMDO) afforded the readily separable crystalline epoxide (**85**) and liquid epoxide (**86**) in the ratio of 5:1, respectively. Recrystallization of (+)-(**85**) gave single crystals.

Having established the absolute configuration of the hydroxy ester (–)-(**82**), the different pathways for the synthesis of 3-methylcarbapentofuranose derivatives (**77**)-(**81**) are outlined in (Scheme **17**). Reduction with $LiAlH_4$ or $VO(acac)_2$-catalyzed hydroxyl-directed epoxidation of (–)-(**82**) afforded diol (–)-(**87**) or epoxide (–)-(**91**) respectively, with excellent yields. These two products were the subunits allowing the synthesis of the different carbasugar derivatives. Starting from the enantiomeric hydroxy ester (+)-(**82**) the other enantiomers of (**77**)-(**81**) are also accessible.

Enantioselective Synthesis of Tochuinyl Acetate (–)-(56)

The marine sesquiterpenes tochuinyl acetate (–)-(**56**) and dihydrotochuinyl acetate (–)-(**93**) were isolated [50] from the dendronotid nudibranch *Tochuina tetraquetra* and also from their feed, the soft coral *Gersemia rubiformis*. These natural products, belonging to the aromatic sesquiterpene cuparene class, possess two stereogenic vicinal quaternary centers in a cyclopentane ring (Fig. **13**).

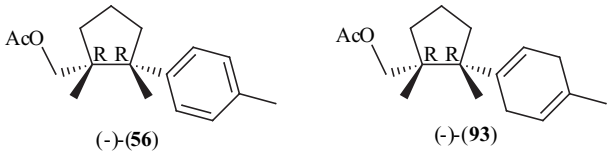
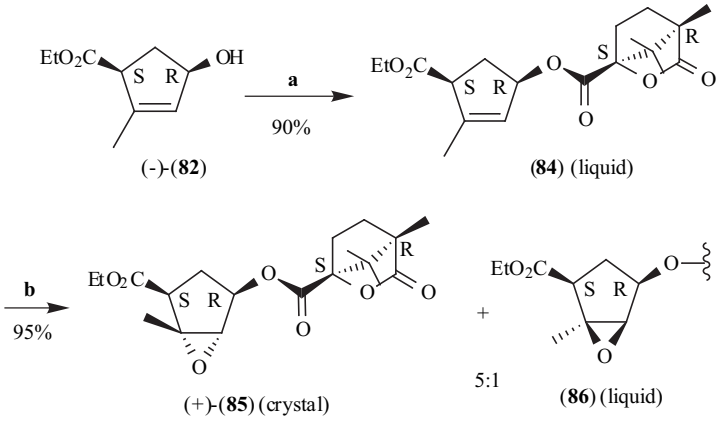


Fig. (13). Natural tochuinyl acetate, (–)-(**56**), and dihydrotochuinyl acetate, (–)-(**93**), are represented with the absolute stereochemistry as determined in our work.

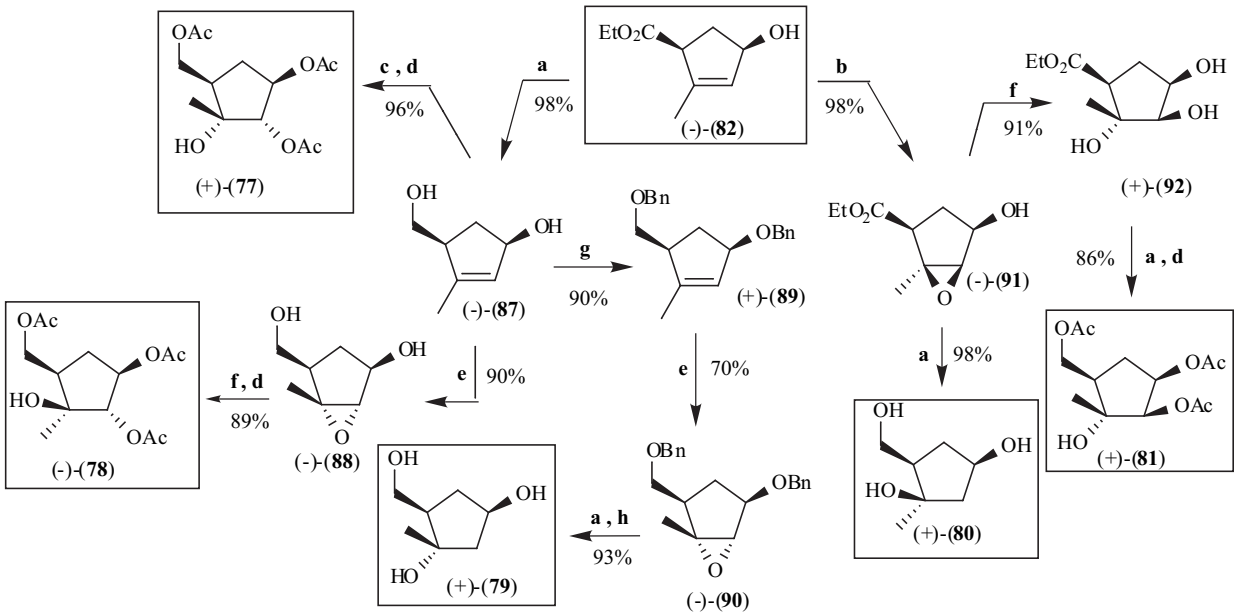
Owing to the difficulty associated with the construction of the adjacent quaternary centers on the sterically congested five-membered ring, their stereoselective synthesis has been a challenge for numerous synthetic organic chemists. So, only racemic syntheses of tochuinyl acetate, (**56**), and dihydrotochuinyl acetate, (**93**), have been published and the absolute configurations still remained unknown [51]. Starting from an enantiopure building block for the introduction and determination of the absolute stereochemistry, we have carried out the first enantioselective synthesis of (–)-(**56**) and (–)-(**93**) and determined the absolute stereochemistry of the two vicinal chiral centers present in the natural products [52]. Our strategy is depicted in Scheme **18**.

The $Ni(acac)_2$-catalyzed 1,4-addition of di-*p*-tolylzinc to ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate furnished stereoselectively the keto ester (±)-(**94**) and $NaBH_4$-$CeCl_3$ Luche reduction of (±)-(**94**) afforded the single stereoisomer (±)-(**95**). With (±)-(**95**) in hand, an efficient enzymatic



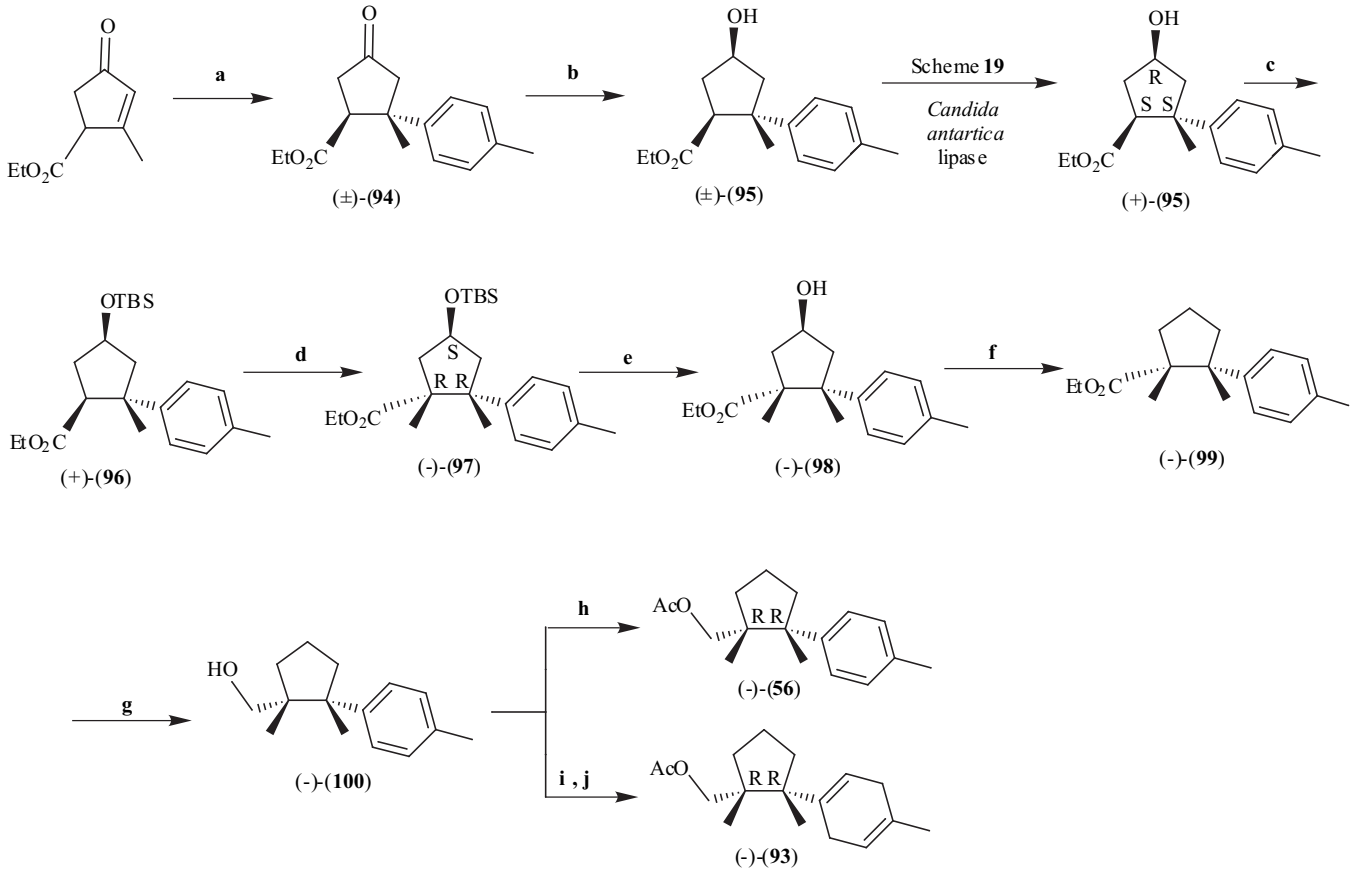
Reagents and conditions: (a) (–)-(1*S*,4*R*)-camphanic acid chloride, DMAP, Py. (b) DMDO, Acetone-H_2O.

Scheme 16. Enantioselective synthesis of crystalline epoxide (+)-(**85**).



Reagents and conditions: (a) $LiAlH_4$, Et_2O; (b) $VO(acac)_2$, *tert*-BuOOH, benzene; (c) OsO_4, NMO; (d) Ac_2O, Py; (e) DMDO, Acetone-H_2O; (f) $HClO_4$, H_2O; (g) NaH, BnBr; (h) Pd/C, H_2.

Scheme 17. Enantioselective synthesis of 3-methylcarbapentofuranose derivatives (**77**)-(**81**).

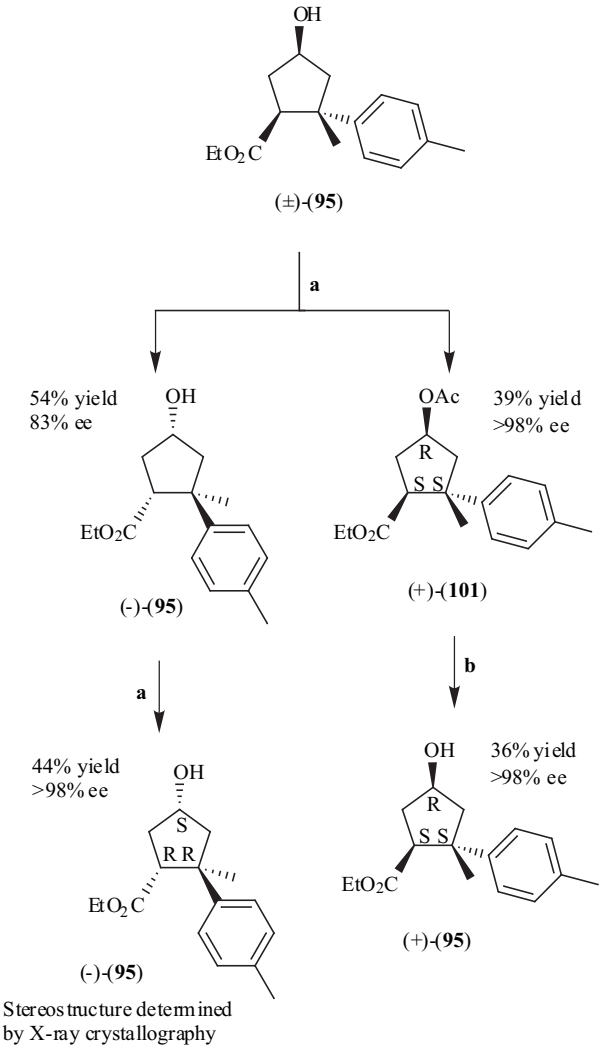


Reagents and conditions: (a) $(p\text{-tol})_2Zn$, $Ni(acac)_2$, Et_2O/THF, rt, 91%; (b) $NaBH_4$, $CeCl_3.7H_2O$, EtOH, 93%; (c) TBSCl, Imidazole, DMF, rt, 100%; (d) LDA, HMPA, MeI, THF, -90°C → rt, 93%; (e) TBAF, THF, rt, 98%; (f) i) NaH, CS_2, MeI, THF, 98%; ii) Bu_3SnH, AIBN, toluene, 96%; (g) $LiAlH_4$, Et_2O, 98%; (h) Ac_2O, pyridine, 95%; (i) Li, NH_3, *t*-BuOH, THF, -40°C; (j) Ac_2O, pyridine, 80% for two steps.

Scheme 18. Enantioselective synthesis of tochuinyl acetate (–)-(**15**) and dihydrotochuinyl acetate (–)-(**93**).

resolution was performed using *Candida antartica* lipase (CAL-B) (Scheme **19**). After 3h of reaction and a standard treatment, the nonreactive alcohol (–)-(**95**) (83% ee) and the acetate (+)-(**101**) (>98% ee) were obtained, respectively, in

54% yield and 39% yield. Acetate (+)-(**96**) was hydrolyzed to afford alcohol (+)-(**95**) in 92% yield (>98% ee, 36% overall yield from racemic (**95**)). The remaining alcohol (−)-(**95**) was resubjected in the same conditions to enzymatic transesterification using the recovered lipase. Alcohol (−)-(**95**) was obtained in 44% overall yield and >98% ee. To establish the absolute configuration of alcohol (−)-(**95**), a X-ray crystallography analysis of its camphanic ester derivative was performed.



Reagents and conditions: (a) CAL-B, vinyl acetate; (b) Na_2CO_3, MeOH, rt, 91%.

Scheme 19. Lipase-catalyzed kinetic resolution of racemic (±)-(**95**).

The secondary alcohol of (+)-(**95**) was protected as its TBS ether (+)-(**96**) and reaction of the lithium enolate of (+)-(**96**) with methyl iodide, furnished the alkylated ester (−)-(**97**) as the sole product. Removal of the TBS protecting group of ester (−)-(**97**) gave the corresponding alcohol (−)-(**98**) and Barton-McCombie deoxygenation of (−)-(**98**) provided the derivative (−)-(**99**) in an overall yield of 94% for the two steps. Finally, reduction of ester (−)-(**99**) to give alcohol (−)-(**100**), followed by acylation, led to (−)-tochuinyl acetate, (−)-(**56**). On the other hand, Birch reduction of alcohol (−)-(**100**) furnished the crude dihydroalcohol, which on acylation using acetic anhydride and pyridine gave (−)-dihydrotochuinyl acetate, (−)-(**93**).

CONCLUSION

Catalysis is one of the most important activities in chemistry and enzymes are among the most selective of catalysts. Now synthetic methods must deal with the increasing constraints imposed by environmental concerns. In this context, we think that combinaison of organic synthesis with biocatalysts will continue to provide efficient routes for the enantioselective synthesis of natural products and this will continue to be the goal of our present and future researches.

ABBREVIATIONS

Ac	=	Acetyl
Bn	=	Benzyl
DIBAL	=	Diisobutylaluminium hydride
DEAD	=	Diethyl azodicarboxylate
DMAP	=	4-Dimethylaminopyridine
DMDO	=	Dimethyldioxirane
DMF	=	*N,N*-dimethylformamide
DMSO	=	Dimethyl sulfoxide
HMPA	=	Hexamethylphophoramide
MCPBA	=	m-chloroperbenzoic acid
Ms	=	Methanesulfonyl (mesyl)
NMO	=	*N*-methylmorpholine oxide
NMR	=	Nuclear magnetic resonance
PPTS	=	Pyridinium *p*-toluenesulfonate
TBAF	=	Tetrabutylammonium fluoride
TBSCl	=	*t*-Butyldimethylsilyl chloride
THF	=	Tetrahydrofuran
p-Tol	=	*p*-Methylphenyl (tolyl)
TPAP	=	Tetrapropylammonium perruthenate
HWE	=	Horner-Wadsworth-Emmons

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Received: July 27, 2004 **Accepted: October 20, 2004**