The first one-pot asymmetric synthesis of esters of highly biologically active (+)- and (−)- 3-[2-(6-methoxynaphthyl)]-2,2-dimethylpentanoic acid (Vallestril®)

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Abstract

Our recent studies on the biological activity of (+)- and (−)-3-[2-(6-hydroxynaphthyl)]-2,2-dimethylpentanoic acid led to several intriguing discoveries that warrant further investigation. As a result it became advisable to provide a straightforward, efficient asymmetric synthesis of these enantiomeric acids. Thus, for the first time, a one-pot asymmetric synthesis of esters of the two acids was designed and carried out, involving Michael addition followed by methylation. With (−)-menthyl as the chiral auxiliary group, 77% of the desired diastereomeric products was obtained, but without stereoselectivity. When the chiral auxiliary group was (−)-8-phenylmenthyl, the yield, based on consumed starting material, was 77%, with a *de* value of 26% determined by ^{1}H NMR.

Further work to optimize the reaction conditions to improve the yield and *de* value is underway.

Keywords: Michael addition, methoxynaphthyldimethylpentanoic acid

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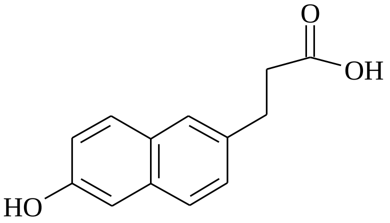
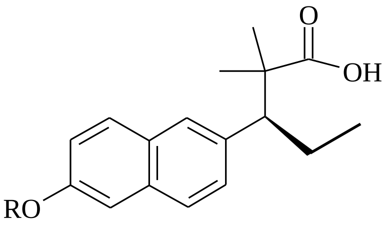
Introduction

In 1947 and 1948, Jacques et al.[1–5] reported the syntheses and biological activity of a series of estrogenic compounds derived from 3-[2-(6-hydroxynaphthyl)]propionic acid (1) (see Structure Block), which was named allenolic acid in honor of Dr. E. Allen (viz. the in vivo Allen−Doisy test for estrogenicity). Of those derivatives of 1, (−)-3-[2-(6-methoxynaphthyl)]-2,2-dimethylpentanoic acid (2) was found to exhibit the most potent estrogenicity in animals, including rats, cats, chicks, and guinea pigs, while the (+) enantiomer (3) showed only one-fifth the estrogenic activity of 2.[6–7] Later, the (−) enantiomer, 2, was marketed by Searle under the trade name Vallestril® for the treatment of postmenopausal symptoms and other estrogen-related problems.[8] Although 2 was highly estrogenic in animals, equivalent to 17β-estradiol (E2), it exhibited far less estrogenicity in women. In clinical trials, high dosages were required to elicit strong estrogenic responses from women,[9–10] and it was eventually taken off the market.[8]

Terenius proposed that 2 was a pro-estrogen and that the true estrogen is its free phenolic form, 4, based on the study he carried out on inhibition of 17β-estradiol uptake on mouse uterus by those compounds.[6] Indeed, Herbai found that in mice, 4 exhibited a 100-fold stronger activity than 2 in inhibiting both weight gain and sulfate incorporation.[7] However, the (+) enantiomer of 4, compound 5, caused significant depression of sulfate incorporation but without the corresponding effects on weight gain.[7] Some years later, Soto, Meyers and Sonnenschein found that while 2 showed very little effect in human MCF-7 cell proliferation, its phenolic form, 4, was found to be highly estrogenic, suggesting that the low estrogenicity of 2 in women is due to human inability to cleave the methyl group from the ethereal oxygen.[11]



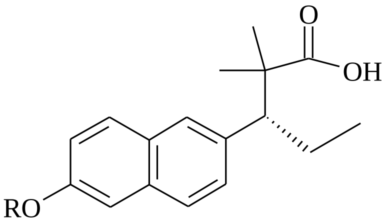
1.



(-)

2. R=CH_3

4. R=H



(+)

3. R=CH_3

5. R=H

Currently, there is tremendous research interest in selective estrogen receptor modulators (SERMs).[12] SERMs have many potential medical applications, such as treating postmenopausal symptoms and preventing osteoporosis, and as hormonal therapy for prostate cancer, while eliminating unwanted side effects. For example, raloxifene, marketed by Eli Lilly and Co. under the trade name Evista®, to prevent osteoporosis in postmenopausal women, has little effect on other reproductive organs. Our recent studies of the physiological effects in rats of 4, 5, and the related (+)- and (−)-*cis*-bisdehydrodoisynolic acids (c*is*-BDDA), indicated that these compounds could be used in a number of therapeutic applications in males and females due to their differential physiological effects on various organs.[13] Most interestingly, in studies with male rats, (+)-BDDA was found to selectively decrease the size of the prostate while having little effect on the physiology of other reproductive organs, such as testis and seminal vesicle.[14] As estrogenic carboxylic acids, 4 and 5 have been shown to have in vitro and in vivo biological profiles similar to those of the corresponding *cis*-BDDA enantiomers, *ie* low binding affinity to cytosolic estrogen receptors when considered in the context of their very high in vivo activity.[15] Clearly, further investigations of the biological effects and mechanism of action of these estrogenic carboxylic acids are necessary.

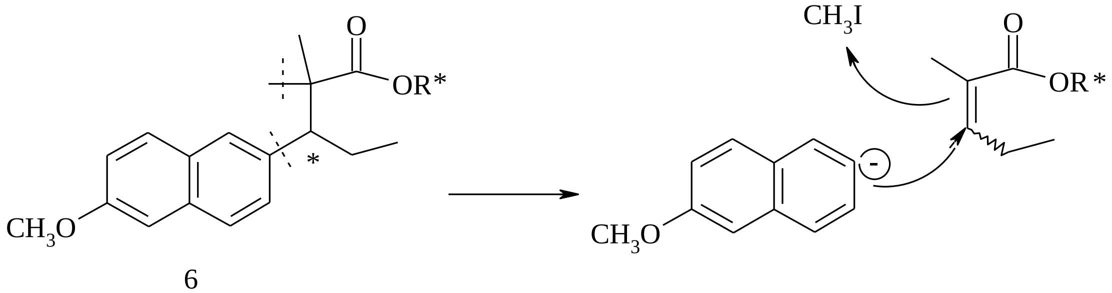
Neither compounds 4 and 5 nor their precursors, 2 and 3, have been commercially available for many years, although these compounds were discovered several decades ago and there are a number of reported methods for preparing the racemic mixture of 2 and 3.[16–20] Most of these methods are multistep processes.[16–18] After each step, the intermediate product must be isolated for use in the next reaction. Ciba Ltd. patented the shortest reported synthesis of racemic 2/3 which proceeded through a coupling reaction of 1-[2-(6-methoxynaphthyl)]-1-chloropropane with ethyl 2-bromo-2-methylpropionate in the presence of zinc.[19–20] Although there is only one step in this process, the yield of the product was not disclosed in the patent; it was probably low due to possible self-coupling reactions. Furthermore, a resolution process[21] would be necessitated to obtain the desired enantiomer for biological testing and therapeutic application and, at best, only 50% of the desired enantiomer would be produced. That is not a commercially viable situation.

To meet the current and forthcoming need for 2 and 3 (and their 6-hydroxy analogs, 4 and 5, respectively) for biological studies and the predicted therapeutic applications for the respective enantiomers, we designed and carried out a one-pot, asymmetric synthesis of the esters of 2 and 3.

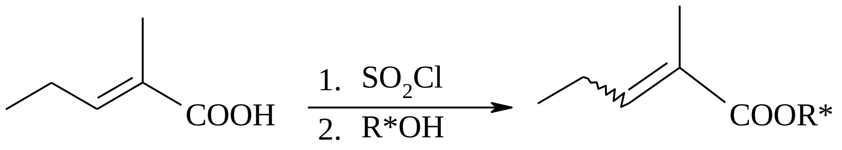
Results and Discussion

Compounds 2 and 3 have an asymmetric center on the benzylic carbon (see Structure Block). Compound 6 can be considered as being composed of three synthons: 6-methoxy-2-naphthyl anion, an ester of 2-methyl-2-pentenoate, and methyl iodide (Scheme 1), and can therefore be synthesized through Michael addition followed by methylation. There are many reports of asymmetric nucleophilic addition to α,β-unsaturated esters.[22] When a chiral auxiliary group R* is used, asymmetric addition to C=C will likely be induced.

As illustrated in Scheme 2, *trans*-2-methyl-2-pentenoic acid (7) was converted into its acid chloride by treatment with thionyl chloride. The acid chloride was then heated with (−)-menthol or (−)-8-phenylmenthol to make compounds 8a or 8b, respectively. Compound 8a was isolated in 75% yield after vacuum distillation, and 8b was isolated in 95% yield via column chromatography. Some *cis-trans* isomerization occurred during the reactions.



Scheme 1

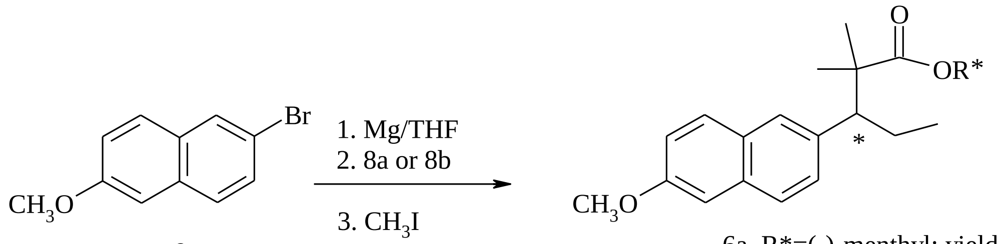


7

8a R*=(-)-menthyl; yield:75%.
8b R*=(-)-8-phenylmenthyl; yield: 95%.

Scheme 2

The diastereomeric esters 6a and 6b were prepared by treating Grignard reagent of 6-methoxy-2-bromonaphthalene (9) with 8a or 8b, respectively, followed by methylation (Scheme 3). It is not surprising that the stereoselectivity in the above reactions was poor, given the fact that Grignard reagents are known to afford low enantioselectivity.[22] However, we feel assured that the use of reagents such as RCu.BF$_3$, will increase the stereoselectivity. For example, Oppolzer and Löher[23] reported the reaction of PhCu.BF$_3$ with (−)-8-phenylmenthyl crotonate in which complete enantioselectivity was achieved. In related work in which they utilized a commercially available chiral sultam (2,10-camphosultam), Oppolzer et al.[24] were able to prepare α-amino acids and similar compounds with extremely high enantioselectivity. We intend to explore the utility of these reagents in our continuing work.



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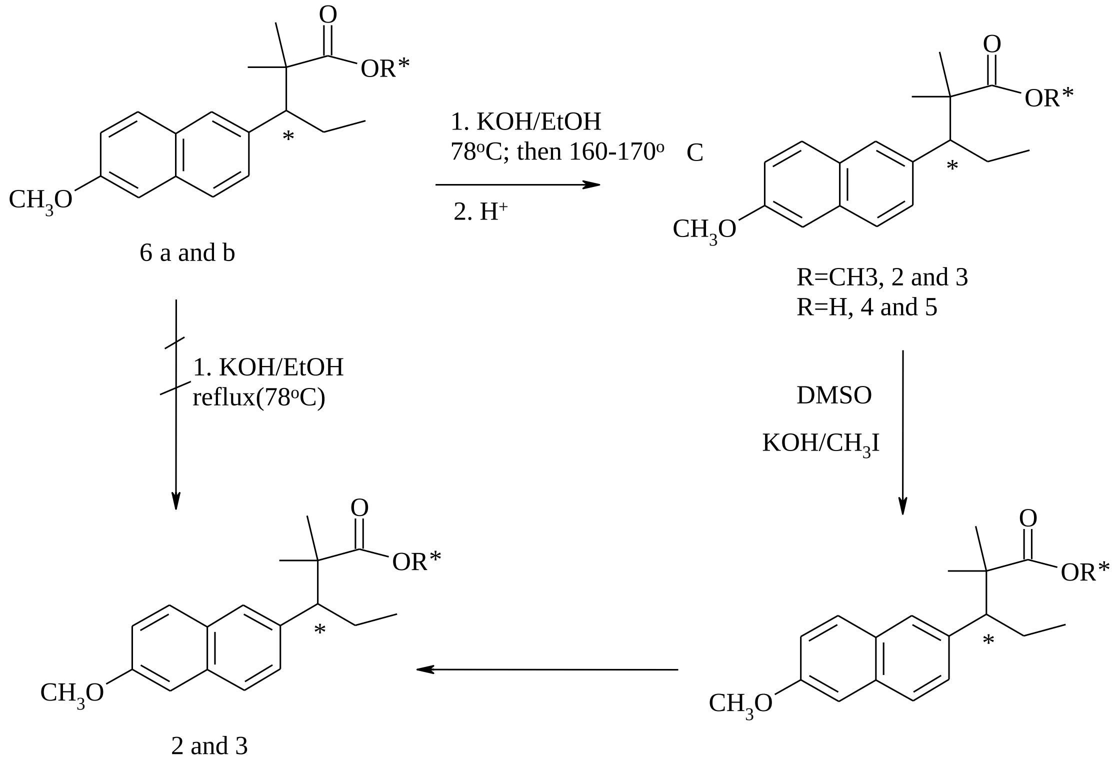
6a. R*=(-)-menthyl; yield, 77%, de, 0.9%
6b. R*=(-)-phenylmenthyl; yield, 77%, de, 26%

Scheme 3

Simply refluxing (78 °C) an ethanolic−KOH solution of 6a or 6b effected no reaction. However, treatment with KOH at 160−170 °C led to complete cleavage of the (−)-menthyl or (−)-8-phenylmenthyl group to form 2 and 3 and some additional cleavage of the 6-methoxy group to form 4 and 5 (Scheme 4).[25] If heating were provided for a longer period, complete conversion to 4 and 5 could be achieved.

This method can also be used to prepare compounds having other substituents on the naphthalene ring or the carboxylic acid side chain.

Experimental Section



Scheme 4

General Procedures. Chemicals were obtained from Aldrich.^{1}H NMR spectra were taken at 300 MHz in $CDCl_3$ solution.

(−)-Menthyl 2-methyl-2-pentenoate (8a). To a 100 mL round-bottomed flask equipped with a stir bar were added 7 (11.4 g, 100 mmol) and thionyl chloride (18 mL, 29.4 g, 247 mmol). Bubbles evolved from the light-yellow solution immediately. The mixture was stirred at rt for 5 min and then heated under reflux for 30 min, during which time the mixture turned brown. Residual thionyl chloride was removed by distillation. (−)-Menthol (15.4 g, 99 mmol) was added to the formed acid chloride, and the mixture was heated in an oil bath (160 ^oC) for 1 h, at which time the evolution of HCl ceased. The mixture was transferred into a separatory funnel and the flask rinsed with hexanes (100 mL) into the funnel. The hexanes solution was washed with aq $NaHCO_3$ solution, then water. The hexanes were removed in vacuo and the residue was vacuum distilled to provide a light yellow oil, 18.7 g; yield: 75%. ^{1}H NMR showed that it was composed of a mixture of *trans*- and *cis*-8a in a ratio of 9:1.

(−)-Menthyl 3-[2-(6-methoxynaphthyl)]-2,2-dimethylpentanoate (6a). To a 25 mL, three-necked round-bottomed flask equipped with a stir bar and a condenser, freshly ground magnesium turnings (0.29 g, 12.1 mmol) were added. The condenser and the flask were sealed with rubber septa, and argon was bubbled into the reaction flask to replace air. To this flask was injected 5 mL of freshly distilled dry THF, after which 1,2-dibromoethane (0.20 mL, 0.43 g, 2.30 mmol) was injected dropwise. The reaction mixture started to reflux shortly without external heating. A solution of 2-bromo-6-methoxynaphthalene (9; 2.37 g, 10 mmol) in a small amount of dry THF was syringed dropwise into the flask at a speed to maintain the reflux. After all the solution was added, the mixture was heated to maintain reflux for 40 min before being cooled in an ice-water bath. A solution of 8a (1.27 g, 3.8 mmol) in 5 mL of dry THF was injected into the flask. The ice-water bath was removed and the mixture was stirred at rt for 1.5 h before methyl iodide (0.62 mL, 1.42 g, 10 mmol) was added via a syringe. After 15 min the reaction was quenched with water. The product was extracted with ether and the ethereal solution was dried over magnesium sulfate. Removal of ether in vacuo left a light yellow oil, 3.33 g. Column chromatography (silica gel, hexanes/ethyl acetate, 50:1) provided a yellow oil, 2.85 g, whose ^{1}H NMR spectrum showed 6a as the major product. Yield by ^{1}H NMR: 77%. The two diastereomers existed in equal amounts.

(−)- And (+)-3-[2-(6-methoxynaphthyl)]-2,2-dimethylpentanoic acid (2 and 3). Absolute ethanol (15 mL), 6a (ca. 2.75 g) from the above experiment, and KOH (5 g) were mixed in a 100 mL round-bottomed flask to form a light-yellow suspension. The mixture was heated in an oil bath at 160−170 ^{o}C to remove the ethanol and held at this temperature for 45 min at which time TLC indicated that no 6a remained. The mixture was cooled to rt and 30 mL of water was added to give a suspension. The suspension was extracted with ether and the aq layer was acidified with 9 M H_2SO_4 and the product was extracted with ethyl acetate. The ethyl acetate solution was dried over $MgSO_4$ and evaporated to dryness to give a thick oil, shown by ^{1}H NMR to be composed of a mixture of 2 and 3 and an approximately equal amount of their 6-hydroxy analogs, 4 and 5. TLC showed two spots as well, matching those of 3 and 5. To the light yellow solution in DMSO (20 mL) of the mixture, 4 g of powdered KOH was added to form a light brown suspension, and to this stirred suspension Me_2SO_4 (2 mL, 2.65 g, 21 mmol) was added. The reaction was exothermic. The mixture was stirred for 15 min and another 2 mL of Me_2SO_4 was added. After another 15 min, water (15 mL) was added to destroy the excess Me_2SO_4 and the product was extracted with ethyl acetate. The ethyl acetate solution was dried and evaporated to dryness to give a brown thick oil, 0.78 g, which was purified through column chromatography (silica gel, hexanes/ethyl acetate, 20:1) to give a light yellow oil, which slowly solidified upon standing. ^{1}H NMR: δ 0.71 (t, 3 H, J = 7.2 Hz), 1.06 (s, 3 H), 1.18 (s, 3 H), 1.62 (m, 1H), 1.89 (m, 1 H), 3.00 (dd, 1 H, J = 3.3, 12.0 Hz), 3.65 (s, 3 H), 3.91 (s, 3 H), 7.12 (s, 1 H), 7.13 (dd, 1 H, J = 2.7, 8.4 Hz), 7.27 (dd, 1 H, J = 1.8, 8.4 Hz), 7.53 (d, 1 H, J = 1.5 Hz), 7.66 (d, 1 H, J = 8.7 Hz), 7.69 (d, 1 H, J = 8.7 Hz).

The methyl ester was dissolved in 30 mL of MeOH and KOH (3 g) was added. The mixture was refluxed for 18 h before being acidified with 9 M H_2SO_4. The product was extracted with ethyl acetate and the solvent dried over $MgSO_4$. Evaporation of the solvent gave a sticky oil, which was recrystallized from hexanes to give 0.48 g of off-white solid; mp 131−131.5 ^{o}C. ^{1}H NMR: δ 0.74 (t, 3 H, J = 7.2 Hz), 1.08 (s, 3 H), 1.19 (s, 3 H), 1.70 (m, 1H), 1.92 (m, 1 H), 3.04 (dd, 1 H, J = 3.0, 12.3 Hz), 3.92 (s, 3 H), 7.12 (s, 1 H), 7.14 (dd, 1 H, J = 2.7, 8.7 Hz), 7.31 (dd, 1 H, J = 1.8, 8.4 Hz), 7.57 (d, 1 H, J = 1.2 Hz), 7.67 (d, 1 H, J = 8.7 Hz), 7.69 (d, 1 H, J = 8.4 Hz). The white solid (0.1145 g) was dissolved in 95% ethanol to make a 25 mL solution, and its optical rotation was measured: $\alpha = +0.001^{o}$. From this value and the reported specific rotation ($[\alpha]^{18}D = +25.5^{o}$)[21] of 3, the *ee* of the (+) enantiomer was determined to be 0.9%.

Preparation of (−)-8-Phenylmenthyl 2-Methyl-2-pentenoate (8b). To a 50 mL round-bottomed flask were added 7 (2.2 g, 19.3 mmol) and thionyl chloride (5 mL, 8.30 g, 70 mmol). Bubbles evolved from the light-yellow solution immediately. The mixture was stirred at rt for 5 min and then heated at reflux for 30 min. Residual thionyl chloride was removed by heating the mixture in an oil bath at 160 °C. (−)-8-Phenylmenthol (0.95 g, 4.1 mmol) was added to the formed acid chloride and the mixture was heated in an oil bath at 190 °C for 30 min Dilute aq KOH solution was added to the mixture and the product extracted with ether. Evaporation of the ether provided a light-brown oil which was purified by column chromatography (silica gel, hexanes/ether, 50:1) to give a light-yellow oil, 1.28 g; yield: 94.8%. ^{1}H NMR showed that it was the desired product which contained some cis isomer, the trans/cis ratio being 5:1.

Preparation of (−)-8-Phenylmenthyl 3-[2-(6-Methoxynaphthyl)]-2,2-dimethylpentanoate (6b). To a 25 mL, three-necked round-bottomed flask equipped with a stir bar and a condenser were added freshly ground magnesium turnings (0.171 g, 7.10 mmol). The condenser and the flask were sealed with rubber septa, and argon was bubbled into the reaction flask to replace air. Into this flask was injected 5 mL of freshly distilled dry THF followed by the dropwise injection of 1,2-dibromoethane (0.18 mL, 0.39 g, 2.10 mmol). The reaction mixture started to reflux shortly, without external heating. A solution of 9 (1.20 g, 5.1 mmol) in dry THF (10 mL) was syringed dropwise into the flask at a speed to maintain the reflux. After all the solution was added, the mixture was heated to maintain reflux for 45 min before being cooled in an ice-water bath. A solution of 8b (1.27 g, 3.8 mmol) in 5 mL of dry THF was injected into the flask. The ice-water bath was removed and the mixture was stirred at rt for 1.5 h before methyl iodide (0.4 mL, 0.91 g, 6.40 mmol) was syringed into the flask. After 15 min the reaction was quenched with aq NH_4Cl solution. The product was extracted with ether, the ethereal solution was dried over magnesium sulfate, and the ether was removed in vacuo to give a light-yellow thick oil. Column chromatography (silica gel, hexanes/ethyl acetate, 50:1 to 20:1) provided a yellow oil, 1.04 g, shown by ^{1}H NMR to be composed of the two diastereomeric esters in a ratio of ca. 1.7:1; *de*, 26%. The yield was 77% based on consumed starting material.

Compound 6b was hydrolyzed according to the procedure described for the hydrolysis of 6a, to provide a mixture of 2 and 3 with an *ee* of 9.2% for the (+) enantiomer (3), calculated as described above.

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