JOC*Note*

Synthesis of *R*-(−)-Imperanene from the Natural Lignan Hydroxymatairesinol

Patrik C. Eklund,* Annika I. Riska, and Rainer E. Sjöholm

Department of Organic Chemistry, Process Chemistry Group, Åbo Akademi University, Piispankatu 8, FIN-20500 Turku, Finland

paeklund@abo.fi

Received May 29, 2002

Abstract: A convenient and high yielding method for the synthesis of *R*-(−)-imperanene, starting from the readily available natural lignan hydroxymatairesinol from Norway spruce, was developed. Hydroxymatairesinol was degraded in strongly basic aqueous conditions to (*E*)-4-(4-hydroxy-3-methoxyphenyl)-2-(4-hydroxy-3-methoxyphenylmethyl)but-3-enoic acid, which was esterified and then reduced by $LiAlH_4$ to afford *R*-(−)-imperanene. The configuration at the crucial stereocenter was preserved in the synthesis, and the obtained product was identified by optical rotation measurements and chiral HPLC analyses as the *R*-(−)-enantiomer (ee 86−92%).

Imperanene (**4**), a phenolic compound belonging to the rare class $C_6-C_4-C_6$ of natural products, has been isolated from rhizomes of the plant *Imperata cylindrica*.[1] Like some other compounds of the $C_6-C_4-C_6$ class,[2−4] imperanene has been shown to have biological activity, including platelet aggregation inhibition. The search for new platelet aggregation inhibitors for the treatment of diseases such as heart attack and stroke is an active research area, in which imperanene could be a potential chemotherapeutic agent.

Recently, Shattuck et al. reported the stereoselective synthesis of both enantiomers of imperanene using chiral auxiliaries.[5] The single enantiomer isolated from *Imperata cylindrica* was thereby shown to be the *S*-(+)-enantiomer by comparison of optical rotation data. More recently, a paper by Doyle et al. reported the synthesis of *S*-(+)-imperanene using asymmetric catalysis, and some concerns regarding the optical rotation were solved.[6]

However, to the best of our knowledge, no paper reporting a high-yielding method for the synthesis of *R*-(−)-imperanene has been published. We here report an alternative, high-yielding semisynthetic method suitable for large-scale preparation of *R*-(−)-imperanene starting from the natural lignan hydroxymatairesinol from Norway spruce (*Picea abies*). Whether or not the (*R*)-enantiomer is a natural product and/or biologically active has hitherto not been established and has to be explored in future investigations. However, the mode of action of both the *R*- and the *S*-enantiomer of imperanene remains unexplored until sufficient quantities of these compounds are obtained.

In 1979 Ekman et al. isolated the compound (*E*)-4-(4-hydroxy-3-methoxyphenyl)-2-(4-hydroxy-3-methoxyphenylmethyl)but-3-enoic acid (**2**) from an acidified alkaline hydrolysate of Norway spruce root extractives. They proved that **2** was formed by the degradation of hydroxymatairesinol (**1**), the most abundant lignan in Norway spruce.[7] Hydroxymatairesinol is found in high concentrations, especially in knots and in the heartwood of branches in Norway spruce.[8] It comprises two diastereomers, namely (7*R*,8*R*,8'*R*)-(−)-7-allo-hydroxymatairesinol (minor isomer) and (7*S*,8*R*,8'*R*)-(−)-7-hydroxymatairesinol (major isomer) (for more information on hydroxymatairesinol see ref 12).

Unlike most other lignans, hydroxymatairesinol can be isolated in large quantities (up to tons) from wood pulping processes.[9] The good availability of hydroxymatairesinol makes it an excellent precursor for the preparation of *R*-(−)-imperanene,[10] which can also be classified as a norlignane, namely (7*E*)-(8'*R*)-(−)-3,3'-dimethoxy-4,4'-dihydroxy-9-norlign-7-en-9'-ol.[11]

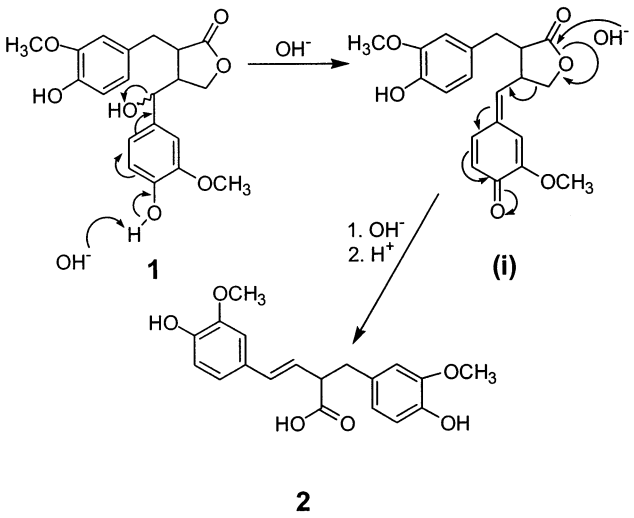
The key step in our method was to achieve a high-yielding step to compound **2**, using hydroxymatairesinol as starting material. When hydroxymatairesinol was stirred in strongly basic conditions (0.6 M NaOH) at 80 °C, compound **2** was obtained after extraction and crystallization in a yield of 80%. The formation of **2** is proposed to proceed via the elimination of formaldehyde from a quinone methide intermediate (**i**) by the mechanism presented in Scheme 1. At strongly basic (pH > 13) conditions, the attack of the hydoxyl ion at the carbonyl carbon seems to initiate the consecutive elimination of formaldehyde and the restoration of the aromatic ring system, besides hydrolyzing the lactone ring. Reactions at milder basic conditions (pH < 13) resulted in non-degraded products with hydrolyzed lactone rings. Attempts to obtain imperanene from the diol (7-hydroxysecoisolariciresinol) obtained by reduction of hydroxymatairesinol with $LiAlH_4$,[12] in a similar manner, were unsuccessful. According to our results, the formation of **2** is depending both on the base strength of the aqueous

* To whom correspondence should be addressed, Fax: +358 2 2154866, Tel: +358 2 215 4502.

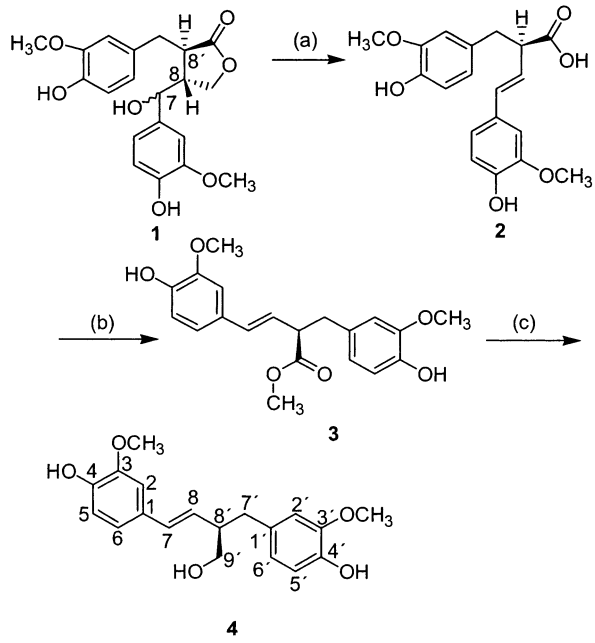
(1) Matsunaga, K.; Shibuya, M.; Ohizumi, Y. *J. Nat. Prod.* **1995**, *58*, 138.
(2) Green, D.; Kashman, Y.; Miroz, A. *J. Nat. Prod.* **1993**, *56*, 1201.
(3) Ishida, M.; Hamasaki, T.; Hatsuda, Y. *Agr. Biol. Chem.* **1979**, *39*, 2181.
(4) Gulavita, N. K.; Pomponi, S. A.; Wright, A. E.; Garay, M.; Sills, M. A. *J. Nat. Prod.* **1995**, *58*, 954.
(5) Shattuck, J. C.; Shreve, C. M. *Org. Lett.* **2001**, *3*, 3021.
(6) Doyle, M. P.; Hu, W.; Valenzuela, M. V. *J. Org. Chem.* **2002**, *67* (9), 2954.
(7) Ekman, R.; Sjöholm, R. T.; Sjöholm, R. *Finn. Chem. Lett.* **1979**, 126.
(8) Willför, S. S.; Hemming, J.; Reunanen, M.; Eckerman, C.; Holmbom, B. *Hydrophilic and lipophilic extractives in Norway spruce knots*, Proceedings 11th International Symposium on Wood Pulping Chemistry, ATIP, Nice, 2001. Willför, S. S.; Hemming, J.; Eckerman, C.; Holmbom, B. *Holzforchung*, **2002**, in press., Ekman R. *Acta Acad. Abo.* Ser. B. **1979**, *39* (3), 1.
(9) Eckerman C.; Holmbom B. Method for recovery of compression wood and/or normal wood from oversize chips, WO 0209893, 2002.
(10) Natural hydroxymatairesinol is isolated as a ca.. 1:3 mixture of diastereomers (8*R*,8'*R*), which are epimers at C-7. However the epimeric center and the stereochemistry at C-8 are destroyed in the first step of the synthesis and only the *R*-enantiomer remains.
(11) Moss, G. P. Nomenclature of lignans and neolignans. *Pure Appl. Chem.* **2000**, *72*, 1493.
(12) Eklund, P. C.; Sillanpää, R.; Sjöholm, R. *J. Chem. Soc, Perkin Trans. 1* **2002**, *16*, 1906.

10.1021/jo025985c CCC: $22.00
Published on Web 09/11/2002

SCHEME 1. Formation of 2 from Hydroxymatairesinol



SCHEME 2[a]



[a] Reagents and conditions: (a) NaOH (0.6 M), 80 °C, 2.5 h; (b) MeOH, H_2SO_4, 50 °C, 17 h; (c) $LiAlH_4$, THF, 20 °C, 3.5 h.

solution and on the butyrolactone ring in the substrate. However, the exact mechanism for the elimination remains to be explored.

Optical rotation measurements[13] and analyses by NMR (homonuclear and heteronuclear direct and long-range chemical shift correlation spectroscopy, COSY, HMQC, HMBC) spectroscopy and chiral HPLC-MS (MRM) confirmed compound **2** to be almost enantiomerically pure *R*-enantiomer having a trans configuration at the double bond. The enantiomeric composition was determined by chiral HPLC-MS (101.6 min for the *R* enantiomer and 117.1 min for the *S* enantiomer), which showed an area relationship of 93:7 and 96:4 varying with reaction conditions, yielding 86−92% ee of **2**.

Compound **2** was then esterified to yield the methyl ester **3** in 80% yield, which was reduced with $LiAlH_4$ to afford (−)-imperanene in ca.75% yield. The conversion of **2** to **3**, followed by reduction was advantageous to the direct reduction of **2** with $LiAlH_4$ (Scheme 2).

Reduction of **3** with $LiBH_4$ gave the same result, but required considerably longer reaction times. The possibility to obtain **3** by transesterification of the lactone ring of hydroxymatairesinol with sodium methoxide was elucidated. However, hydroxymatairesinol did not undergo transesterification and elimination to afford **3** when treated with a large excess of sodium methoxide in methanol. Instead, 7-methoxymatairesinol was formed, probably by a nucleophilic addition to the quinone methide (unpublished results). This supported a quinone methide as the key intermediate in the formation of **2** from **1** under alkaline conditions.

In conclusion, *R*-(−)-imperanene was synthesized in high enantiomeric purity (ee ∼ 90%) starting from the readily available spruce lignan hydroxymatairesinol in three steps with an overall yield of approximately 60% without fully optimized conditions. The comparison of the optical rotation of **4** with that of the stereoselectively synthesized *R*-(−)-imperanene[5] confirmed the fact that the stereocenter is preserved and only slight inversion of the configuration at C-8' occurs during the synthetic transformations. As a consequence, also the *R* configuration at C-8' in hydroxymatairesinol was confirmed unambiguously.

(13) We obtained a specific rotation, $[\alpha]^{25}_D = -144°$ ($c = 0.01$ g/mL, EtOH), −103° ($c = 0.003$ g/mL, $CHCl_3$) for *R*-(−)-imperanene, which differs markedly from the value given in ref 5, (82−90% ee) $[\alpha]^{25}_D = -633°$ ($c = 0.01$ g/mL, $CHCl_3$). However, our ^1H and ^{13}C NMR spectra were almost identical with those reported in ref 1 for *S*-(+)-imperanene and those reported in ref 5 for *S*-(+)-imperanene and *R*-(−)-imperanene, respectively (The small differences may be due to different sample concentrations). The purity of our sample was ≥98% and 90% ee according to GC and chiral HPLC-MS. However, very recently Doyle et al.[6] reported an [α] value of +103° ($c = 1.7$ $CHCl_3$) and +97° ($c = 0.68$ $CHCl_3$) for synthetic *S*-(+)-imperanene, and the questions regarding optical rotations were discussed.

Experimental Section

All commercially available chemicals were used as supplied by the manufacturers. Hydroxymatairesinol was isolated from Norway spruce knots by the methods described in refs 8 and 9. Knots of Norway spruce were separated, ground, and freeze-dried prior to extraction in a Soxhlet apparatus. The raw extract obtained with acetone−water (9:1 v/v), after the removal of lipophilic extractives with petroleum ether, was purified by flash chromatography (eluent $CHCl_2$:EtOH 98:2 v/v) to yield hydroxymatairesinol.

GC analyses were performed on a standard gas chromatograph equipped with a HP-5 column and a FI detector. The samples were silylated using hexamethyldisilazane−chlorotrimethylsilane in pyridine, prior to analyses.

^1H and ^{13}C spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively. 2D experiments (COSY, HMQC, HMBC, COLOC) were recorded using standard pulse sequences, and chemical shifts are reported downfield from tetramethylsilane.

Optical rotations were measured with a digital polarimeter, using a 1 dm, 1 mL cell. Preparative chromatography was performed on a MPLC apparatus, using normal phase silica (silica gel 40, ≥ 400 mesh, 600 m^2/g). Analytical TLC was carried out on precoated aluminum-backed sheets. Chiral HPLC-MS was performed on an analytical column (0.46 × 25 cm) using multiple reaction monitoring techniques (MRM).

(3*E*)-4-(4-Hydroxy-3-methoxyphenyl)-2-(4-hydroxy-3-methoxyphenylmethyl)but-3-enoic Acid (2). Aqueous NaOH (0.6 M, 200 mL) was heated to 50 °C, and hydroxymatairesinol

(1.530 g, 4.1 mmol) was added. The temperature was adjusted to 80 °C, and the solution was stirred for 2.5 h, cooled to room temperature, and acidified with HCl solution (6 M) to pH ∼ 1. The mixture was then extracted with dichloromethane (4 × 50 mL), and the organic phase was dried over Na_2SO_4. Evaporation of the solvent, using a rotary evaporator, left a light yellow solid (1.386 g, 98%) of **2** in a purity of 94% (GC). Crystallization from dichloromethane:diethyl ether (3:1) gave **2** as white needles (1.068 g, 80%) in a purity of 98% (GC). Mp 126−128 °C, $[\alpha]^{22}_D$ −113° (c = 0.03 g/mL, C_2H_5OH), 90% ee (HPLC).

HRMS m/z calculated for $C_{19}H_{20}O_6$ (M^+) 344.1260 found 344.1264. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (1H, dd, J = 13.8, 6.9 Hz), 3.11 (1H, dd J = 13.7, 7.8 Hz), 3.41 (1H, dddd, J = 8.7, 7.9, 7.0, 0.9 Hz), 3.78 (3H, s), 3.88 (3H, s), 6.08 (1H, dd, J = 15.8, 8.8 Hz), 6.36 (1H, d, J = 15.4 Hz), 6.69 (1H, dd, J = 7.9, 2.0 Hz), 6.72 (1H, d, J = 1.9 Hz), 6.79 (1H, d, J = 7.9 Hz), 6.81−6.88 (3 H, m, complex). ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.7, 51.6, 55.9, 55.9, 108.6, 112.1, 114.5, 114.7, 120.2, 121.9, 124.5, 129.4, 130.5, 132.7, 144.4, 145.8, 146.6, 147.0, 176.9. EIMS m/z (relative intensity) 344 (13), 298 (5), 207 (5), 161 (7), 150 (12), 137 (100), 122 (2), 71 (6).

Methyl (3*E*)-4-(4-Hydroxy-3-methoxyphenyl)-2-(4-hydroxy-3-methoxyphenylmethyl)but-3-enoate (3). 2 (purity 98%, 0.554 g, 1.6 mmol) was dissolved in 55 mL of methanol, and 0.1 mL of 4:1 methanol−concentrated H_2SO_4 (0.36 mmol) was added. The solution was stirred for 17 h at 50 °C and then poured into 70 mL of saturated NaCl solution. The mixture was extracted with dichloromethane and the organic phase dried over Na_2SO_4. Evaporation of the solvent gave 0.569 g (99%) of **3** in a purity of 93% (GC). Crystallization from dichloromethane−ether (1:1) gave 0.40 g (70%) of **3** as a yellow solid. Mp. 143−144 °C. $[\alpha]^{22}_D$ −129° (c = 0.02 g/mL, C_2H_5OH), purity by GC 97%, ee 90% (HPLC).

HRMS m/z calculated for $C_{20}H_{22}O_6$ (M^+) 358.1416 found 358.1422. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (1H, dd, J = 13.7, 6.9 Hz), 3.08 (1H, dd J = 13.7, 8.1 Hz), 3.40 (1H, dddd, J = 8.9, 8.0, 6.9, 0.8 Hz), 3.65 (3H, s), 3.81(3H, s), 3.88 (3H, s), 6.06 (1H, dd, J = 15.8, 8.8 Hz), 6.32 (1H, d, J = 15.9 Hz), 6.66−6.69 (2H, m, complex) 6.81 (1H, d, J = 8.5 Hz), 6.80−6.86 (3H, m, complex). ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.9, 51.7, 51.9, 55.9, 55.9, 108.2, 111.8, 114.3, 114.4, 120.2, 121.8, 124.6, 129.3, 130.6, 132.5, 144.2, 145.6, 146.3, 146.7, 174.2. EIMS m/z (relative intensity) 358 (17), 299 (3), 222 (16), 190 (7), 175 (29), 161 (25), 137 (100), 122 (3).

***R*-(−)-Imperanene (4). 3** (1.5 mmol, 0.554 g, purity 96%) was dissolved in 40 mL of dry THF, and LAH (0.367 g, 9.7 mmol) was portionwise added. The mixture was stirred at room temperature under an atmosphere of argon (flame-dried glassware) for 3.5 h. The reaction was then quenched by adding the reaction mixture to 100 mL of distilled water. The pH value was adjusted to 6 with 10% HCl, and the mixture was extracted with dichloromethane (3 × 50 mL). The organic phase was washed with 50 mL of saturated NaCl solution and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was dried under vacuum, yielding 0.424 g (83%) of **4** as a white powder. Purity 94%. The product was further purified by MPLC (ethyl acetate:petroleum ether, 1:1) to yield 0.266 g (54%) of **4** in a purity ≥ 98% (GC), 90% ee (HPLC), $[\alpha]^{22}_D$ −144° (c = 0.01 g/mL, C_2H_5OH), −103° (c = 0.003 g/mL, $CHCl_3$).

HRMS m/z calculated for $C_{19}H_{22}O_5$ (M^+) 330.1467 found 330.1470. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (1H, m), 2.68 (1H, dd, J = 13.4, 7.0 Hz) 2.74 (1H, dd, J = 13.4, 7.2 Hz), 3.56 (1H, dd, J = 10.7, 7.2 Hz), 3.66 (1H, dd, J = 10.6, 4.7 Hz), 3.81 (3H, s), 3.88 (3H, s), 5.54 (1H, s), 5.68 (1H, s), 5.92 (1H, dd, J = 16.0, 8.3 Hz), 6.34 (1H, dd, J = 15.9, 0.8 Hz), 6.66 (1H, dd, J = 8.2, 2.0 Hz), 6.68 (1H, complex), 6.81 (1H, d, J = 8.2 Hz), 6.80−6.85 (3H, complex). ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.7, 47.6, 55.9, 55.9, 65.3, 108.3, 111.8, 114.2, 114.5, 119.7, 121.9, 128.4, 129.8, 131.5, 132.1, 143.9, 145.3, 146.3, 146.6. EIMS m/z (relative intensity) 330 (41), 312 (14), 210 (21), 193 (49), 175 (58), 151 (54), 143 (17), 137 (100).

Acknowledgment. The authors thank Hormos Nutraceutical Ltd., Turku, Finland, for the financial support of this work, Mr M. Reunanen, Laboratory of Forest Product Chemistry, Åbo Akademi University, Turku, Finland, for the HRMS analyses, Mr. C. Eckerman, Laboratory of Forest Product Chemistry, Åbo Akademi University, Turku, Finland, for the supply of hydroxymatairesinol, and Annika Smeds, Department of Organic Chemistry, Åbo Akademi University, Turku, Finland, for the Chiral HPLC-MS analyses.

JO025985C