Tetrahedron Letters,Vol.30,No.31,pp 4141-4144,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

GENERAL ENTRY TO THE SYNTHESIS OF OPTICALLY ACTIVE DITERPENOIDS OF C-20β SERIES

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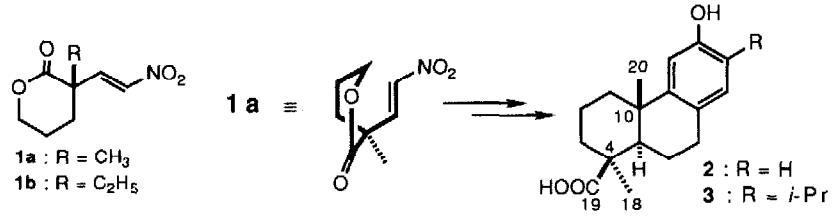
Abstract: (+)-Podocarpic acid (**2**) and (+)-lambertic acid (**3**) were synthesized from (*S*)-(-)-nitroolefin **1a**.

Recently we reported an efficient asymmetric synthesis of chiral building blocks **1** based on an addition-elimination reaction.[1] The chiral building block **1b** has been shown to be a suitable starting material for the syntheses of optically active indole alkaloids of *Aspidosperma*- and *Hunteria*-type.[2] Here we describe a general entry to the syntheses of optically active diterpenoids of podocarpane- and abietane-type using **1a** as a chiral building block.

A huge number of diterpenoids with a carboxyl group as C-19 functionality have been isolated. The nitroolefin **1a** is an appropriate starting material for this type of diterpenoids, because **1a** has all carbon atoms of ring A as well as the correct absolute stereochemistry at C-4 in these diterpenoids such as podocarpic acid (**2**), as illustrated in Scheme I. Thus, treatment of the (*S*)-(-)-nitroolefin **1a** of

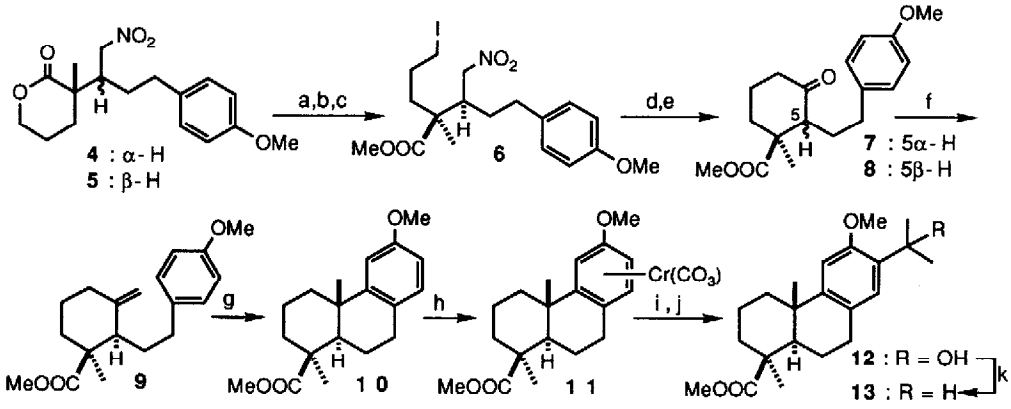
Scheme I.



91% enantiomeric excess (ee) with 2-(4'-methoxyphenyl)ethyl magnesium iodide afforded a 3 : 2 mixture of **4** and **5** in 77% yield. The lactone ring in the major isomer **4** was opened with sodium methoxide in methanol to give a hydroxy ester which was further converted into the iodide **6** by mesylation followed by the substitution with sodium iodide in 87% overall yield from **4**. Intramolecular alkylation of **6** and the successive Nef reaction with $TiCl_3/NH_4OAc$ provided a cyclohexanone **7** in 55% yield. The minor isomer **5** was converted into **8** in 40%

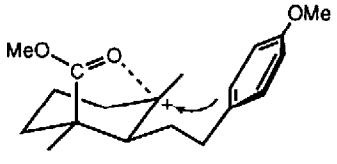
overall yield through the same sequence of the reactions for **4**. Since **7** and **8** were shown to establish an equilibrium in the ratio of 1 : 1 with *p*-toluenesulfonic acid in refluxing methanol, 5*S*-isomer **7** could be obtained from the minor isomer **5**. Methylenation of **7** by Nozaki's mehod[3] gave **9** in 85% yield without epimerization at C-5, while epimerization occurred under the normal Wittig conditions ($Ph_3P{=}CH_2$/*t*-BuOK). Treatment of **9** with modified polyphosphoric acid ($MeSO_3H$-P_2O_5)[4] afforded a 92% yield of methyl *O*-methylpodocarpate (**10**), mp. 129-130.5 °C, $[\alpha]_D$ +128° ($CHCl_3$).[5] The desired trans A/B-ring juncture with *S*-configuration at C-10 can be explained by the neighboring group participation of the methoxycarbonyl group shown in Figure 1. Since the bulky β-arylethyl group should take equatorial conformation in the intermediate carbenium ion , the methoxycarbonyl group is automatically disposed axially to participate with the cationic center. A combination reagent system of aluminum bromide and ethanethiol[6] cleaved both the methyl ether and the ester to give (+)-podocarpic acid (**2**)[7] in 98% yield.

Scheme II.



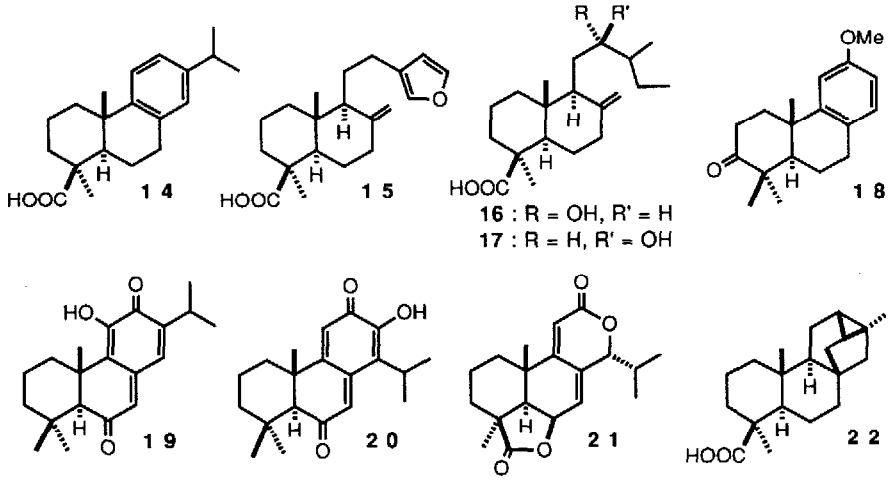
a) NaOMe. b) MsCl. c) NaI. d) NaH in DMF. e) MeONa in MeOH, then $TiCl_3/NH_4OAc$. f) CH_2Br_2/Zn /$TiCl_4$. g) $MeSO_3H/P_2O_5$. h) $Cr(CO_6)$. i) *n*-BuLi/acetone. j) Pyridine/refl. k) Et_3SiH/CF_3COOH.

Figure 1. Intermediate for the conversion of **9** into **10**.



Treatment of methyl *O*-methylpodocarpate (**10**) with chromium hexacarbonyl in refluxing dibutyl ether for 24h afforded a 2 : 1 mixture of

chromium complex **11** in 92% yield. Lithiation[8] of **11** with *n*-BuLi was followed by the addition of acetone to furnish **12** in 55% yield after decomplexation in refluxing pyridine. Reductive removal of hydroxyl group in **12** was accomplished by ionic hydrogenation with Et_3SiH/CF_3COOH[9] to give **13** (92%), which was converted into (+)-lambertic acid (**3**) [mp. 252-254 °C, $[\alpha]_D$ +127° (EtOH), lit.[10] mp. 252-254 °C, $[\alpha]_D$ +121.5° (EtOH)] in 82% yield by demethylation with a combination system of aluminum chloride and ethanethiol.[6]



Since methyl *O*-methylpodocarpate (**10**) has been converted into callitricic acid (**14**)[11] and lambertianic acid (**15**),[12] the synthesis of (+)-**10** constitutes the formal total syntheses of those diterpenoids in optically active form. Methyl (12*S*)- and (12*R*)-hydroxylabd-8(17)-en-19-oates (**16** and **17**),[13] hinokino methyl ether (**18**),[14] taxodione (**19**),[15] maytenoquinone (**20**),[16] nagilactone F (**21**),[17] and trachiloban-19-oic acid (**22**)[18] were derived from natural podocarpic acid (**2**), synthesis of **2** again forms the total synthesis of those diterpenoids though in a formal sense.

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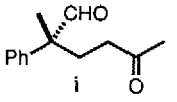

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(Received in Japan 11 May 1989)