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Use of Dihydroquinidine 9-O-(9'-Phenanthryl) Ether in Osmium-Catalyzed Asymmetric Dihydroxylation in the Synthesis of Brassinosteroids

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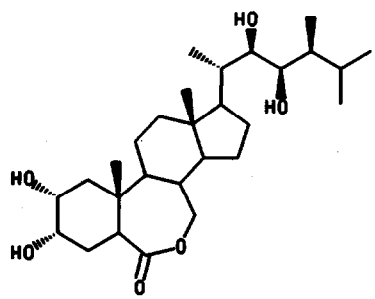
Key Words: Brassinosteroids; Plant Hormones; Osmium Tetroxide; Asymmetric Dihydroxylation; Dihydroquinidine 9-O-(9'-Phenanthryl) Ether

Abstract: *The 22R,23R-homobrassinosteroid analogs are obtained in good yield from the corresponding precursor with a 22E-double bond by osmium-catalyzed asymmetric dihydroxylation using dihydroquinidine 9-O-(9'-phenantryl) ether (DHQD PHN) as chiral agent.*

Since the discovery of brassinolide (1), a new plant growth promoter, much efforts have been spent to synthesize its analogs.



1

The usual method for synthetizing brassinosteroid analogs involves the introduction of the required functional groups in the rings A and B and in the side chain starting from an available steroid (stigmasterol, ergosterol or brassicasterol). All these commertial starting materials have a Δ^{22} double bond. Cis-hydroxylation is commonly accomplished by osmium-catalyzed reaction which gives a mixture of (22R,23R) and (22S,23S)-isomers, the latter being the major one, particularly when an alkyl substituent (24S) is present[1]. However, the (22R,23R)-isomers are the natural compounds and the most active as plant growth regulators[2].

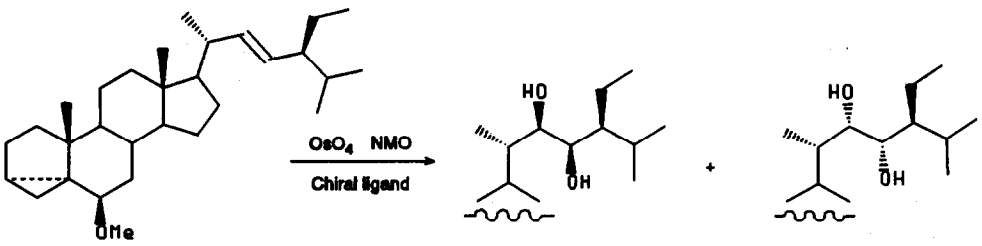
In the homobrassinolide analogs (24S-ethyl), this ratio is shifted to the unwanted (22S,23S)-isomer giving almost exclusively this product[3]. It leads to a very important decrease in the total yield of the synthesis of such compounds.

As it has been reported[4], the use of dihydroquinidine alkaloid derivatives as ligands in osmium-catalyzed dihydroxylation, induces the formation of the RR enantiomers.

In 1991 this procedure was published[5] for the dihydroxylation of 22(E)-methyl hyodeoxycholate, that lacks the C-24 alkyl substituent, by using dihydroquinidine p-chlorobenzoate (DHQD CLB) as chiral ligand and affording a 4:1 mixture of the (22R,23S) and (22S,23R) diols. These compounds were then used in the synthesis of brassinolide analogs. More recently[6], the same authors applied this methodology to the dihydroxylation of Δ^{22} double bond in brassinosteroid analogs with a (24S)-methyl or ethyl groups and (24R)-methyl group. Using steroids with a (24S)-ethyl substituent, they obtained a diol ratio (22R,23R):(22S,23S) of 1.5:1 under the best conditions.

We wish to report now our results in the osmium-catalyzed asymmetric dihydroxylation of steroids (**2** and **3**) with a Δ^{22} double bond and a (24S)-ethyl group using dihydroquinidine 9-O-(9'-phenanthryl) ether (DHQD PHN) as chiral ligand[7]. For the same substrate **3**, the ratio (22R,23R):(22S,23S) is improved to 2.6:1 using DHQD PHN compared to 1.3:1 ratio as previously reported by Zhou[6] with DHQD CLB.

The study of the experimental conditions to afford the best (22R,23R):(22S,23S)[8] ratio has been done on (22E)-3α,5-cyclo-6ß-methoxystigmast-22-en (**2**)[9] as substrate, DHQD CLB and DHQD PHN as chiral ligands and *N*-methylmorpholine *N*-oxide (NMO) as reoxidant.



2 (22R,23R) **6** (22S,23S) **7**

Scheme 1

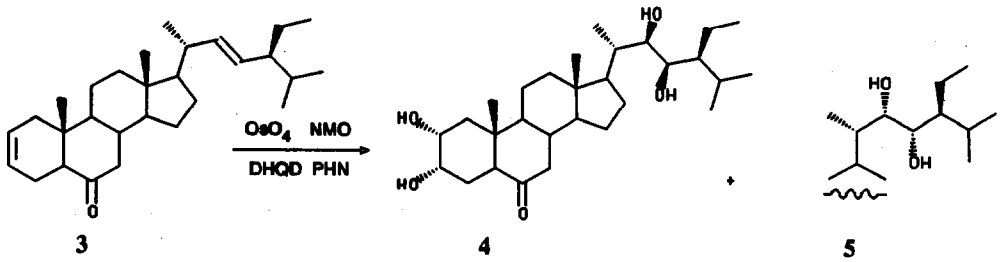
The results obtained (**Table 1**) show that the osmium-catalyzed asymmetric dihydroxylation of (22E)-3α,5-cyclo-6ß-methoxystigmast-22-en (**2**) (**Scheme 1**), using either DHQD CLB or DHQD PHN derivatives, has led to a large increase in the proportion of the (22R,23R)-stereoisomer, compared to the one obtained with no chiral ligand.

Table 1. Results obtained in the dihydroxylation of **2**.

conditions	room temperature			slow add. r.t.	slow add. 0°C	slow add. 0°C[a)]
ligand	without	DHQD CLB	DHQD PHN	DHQD PHN	DHQD PHN	DHQD PHN
ratio (22R,23R):(22S,23S)	1:24	1:2.6	1:1.5	1.1:1	1.5:1	2.2:1

[a)] Double amounts of OsO_4 and DHQD PHN are used.

From both chiral ligands, DHQD PHN gave the best results under the same experimental conditions (r.t.) (1:1.5 against 1:2.6). In order to improve further the stereoselectivity we have tried different experimental conditions: olefin addition, temperature and amount of OsO_4 and DHQD PHN. The stereoselectivity is greatly enhanced (2.2:1) carrying out the reaction at 0°C, adding the olefin for one hour and using 0.2 eq of OsO_4 and 2 eq of DHQD PHN per 1 eq of **2** (see **Table 1**).



3 **4** **5**

Scheme 2

Taking into account that the homocastasterone (**4**), that possesses a 22R,23R,24S stereochemistry, is a natural brassinosteroid with an important bioactivity, we have applied this methodology to its synthesis (**Scheme 2**). Thus, by treating (22E)-stigmasta-2,22-dien-6-one (**3**)[10] with OsO_4 (0.1 eq.), NMO (30 eq.) and DHQD PHN (1 eq.) we have obtained the homocastasterone (**4**) and its (22S,23S)-isomer (**5**) in 76% yield after 5 days with a ratio (22R,23R):(22S,23S) of 2.6:1. This result represents an improvement of the synthesis of homocastasterone (**4**) over the previous reported by Zhou[6] who obtained **4** and **5** with a 1.3:1 (22R,23R):(22S,23S) ratio using DHQD CLB as chiral ligand and $K_3Fe(CN)_6$ as reoxidant.

General procedure:

The treatment of the olefin (1eq.) with NMO (30 eq.) and osmium tetroxide (0.1 eq.) in solution of THF:t-BuOH:H_2O (7.2:4:1.1), and the chiral ligand (1 eq.) when used, after 4-5 days of reaction at r.t. in the dark, gives a mixture of (22R,23R) and (22S,23S) diols (80% yield). The composition of the reaction mixture is determined by HPLC analysis using a LiChrospher RP-18 column and acetonitrile (for substrate **2**) or acetonitrile/water 50:50 (for substrate **3**) as eluent. The compounds are isolated by column chromatography on silica gel (n-hexane/AcOEt 5:1 for substrate **2** and n-hexane/AcOEt 1:6 for substrate **3**).

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8. (22R,23R)-3α,5-cyclo-6ß-methoxystigmasta-22,23-diol (**6**).
   ^{1}H-RMN (200 MHz,$CDCl_3$): δ 3.73+3.61 (2H, 2d, J=8.7Hz, J=8.7Hz, H-C22+H-C23), 3.33 (3H, s, OCH_3), 2.78 (1H, dd, J=2.7Hz, αH-C6), 1.03 (3H, s, 19-CH_3), 0.97+0.96 (6H, 2d, J=6.8Hz, J=6.8Hz, 26-CH_3+27-CH_3), 0.94 (3H, d, J=7.2Hz, 21-CH_3), 0.92 (3H, t, J=6.1Hz, 29-CH_3), 0.73 (3H, s, 18-CH_3).
   ^{13}C-RMN (50 MHz, $CDCl_3$): δ 82.4 (d, C6), 74.7+72.7 (2d, C22+C23), 56.5 (q, O$\underline{C}H_3$), 56.3 (d, C14), 52.6 (d, C17), 47.8 (d, C24), 46.1 (d, C9), 43.2 (s, C13), 42.5 (s, C5), 40.1 (t, C12), 36.8 (d, C20), 35.1 (q, C10), 34.9 (t, C7), 33.2 (t, C1), 30.4 (d, C8), 28.7 (d, C25), 27.7 (t, C16), 24.8 (t, C2), 23.9 (t, C15), 22.6 (t, C11), 21.3 (d, C3), 21.1 (q), 19.2 (q), 19.1 (q), 18.7 (t, C28), 13.2 (q), 12.9 (t, C4), 11.9 (q), 11.7 (q).
   (22S,23S)-3α,5-cyclo-6ß-methoxystigmasta-22,23-diol (**7**).
   ^{1}H-RMN (200 MHz, $CDCl_3$): δ 3.69-3.54 (2H, m, H-C22+H-C23), 3.33 (3H, s,OCH_3), 2.78 (1H, dd, J=2Hz, J=2Hz, αH-C6), 2.43-2.25 (2H, br.s, C22-OH+C23-OH, dissappears after shaking with D_2O), 1.05-0.98 (6H, m, 29-CH_3+21-CH_3), 1.02 (3H, s, 19-CH_3), 0.94+0.87 (6H, 2d, J=6.9Hz, J=6.8Hz, 26-CH_3+27-CH_3), 0.76 (3H, s, 18-CH_3).
   ^{13}C-RMN (50 MHz, $CDCl_3$): δ 82.3 (d, C6), 72.0+70.4 (2d, C22+C23), 56.5 (q,O$\underline{C}H_3$), 56.0 (d, C14), 52.6 (d, C17), 49.5 (d, C24), 47.8 (d, C9), 43.2 (q, C13), 43.1 (q, C5), 42.4 (d, C20), 40.0 (t, C12), 35.0 (q, C10), 34.9 (t, C7), 33.2 (t, C1), 30.3 (d, C8), 27.9 (t, C16), 26.7 (d, C25), 24.8 (t, C2), 24.2 (t, C15), 22.6 (t, C11), 21.6 (q, C29), 21.2 (d, C3), 19.1 (q, C19), 18.2 (t, C28), 17.5 (q, C27), 14.3 (q, C26), 13.8 (q, C21), 12.9 (t, C4), 11.9 (q, C18).
9. The synthesis of (22E)-3α,5-cyclo-6ß-methoxystigmast-22-en (**2**) is accomplished following the procedure described by J.A Steele, E. Mosettig (*J. Org. Chem.* **1963**, *28*, 571). The overall yield has been improved up to 78% compared to the previously reported (66%). Also we have isolated (22E)-3ß-methoxystigmasta-5,22-diene with a 8% yield as a secondary product.
10. The synthesis of (22E)-stigmasta-2,22-dien-6-one (**3**) following the procedure descrived by M. Aburatani *et al.* (Synthesis **1987**, 181) was accomplished with a 61% yield from stigmasterol.

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