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Practical, efficient, stereoselective, formal synthesis of (2*R*,3*R*,4*R*)-3-hydroxy-4-methylproline☆

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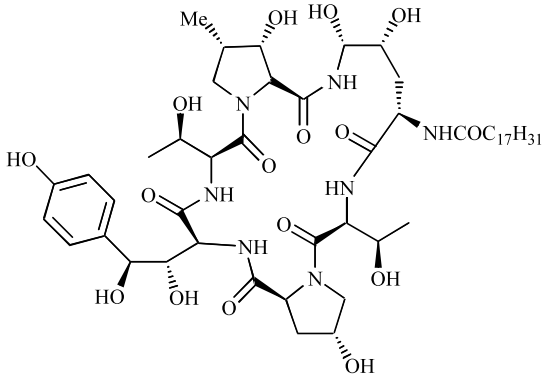
Abstract—A highly efficient and stereoselective synthesis of (2*R*,3*R*,4*R*)-HMP is disclosed employing the sulfinyl group as an internal nucleophile to functionalize an olefin in the key step of the reaction sequence. The proline ring is elaborated by a (4C+N) cyclization.

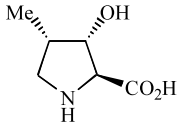
Antimicrobial cyclic peptides, echinocandins (**1**),[1] pnuemocandins, sporiofungin A and mulundocandin[2] have in common, an unusual amino acid, (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline (HMP) (**2**) as one of their constituents. An efficient route to HMP[3] would be useful in the preparation of analogs of the antifungal lipopeptides.[4] In connection with our interest in elaborating key intermediates by heterofunctionalization of olefins exploiting the sulfinyl moiety as the internal nucleophile,[5] we detail herein an efficient and stereoselective synthesis of (2*R*,3*R*,4*R*)-HMP (**3**).

The synthesis of **3** was envisaged by a (4C+N) cyclization of the retron (**4**) (Scheme 1, retrosynthetic analysis), which in turn can be derived from the bromohydrin (**5**), readily obtained from olefin (**6**).

The synthesis of **6** (P^1 = TBDPS) began with the ester (**7**).[6] Reduction of **7** with alane, generated in situ, afforded allyl alcohol (**8**) which on oxidation by treatment with $NaIO_4$ afforded an equimolar mixture of sulfoxides (**9**). Protection of the primary hydroxy group as its *t*-butyldiphenylsilyl ether afforded **6** which could be separated as individual diastereomers. Since we had earlier demonstrated that the sulfoxide configuration had no influence on the stereoselectivity of bromohydration,[5b] no efforts were made to separate the diastereomers. Treatment of the allyl ether (**6**) with



1, Echinocandin B



2, HMP

Keywords: sulfoxide; hydroxymethyl proline; bromohydrin; stereoselective.
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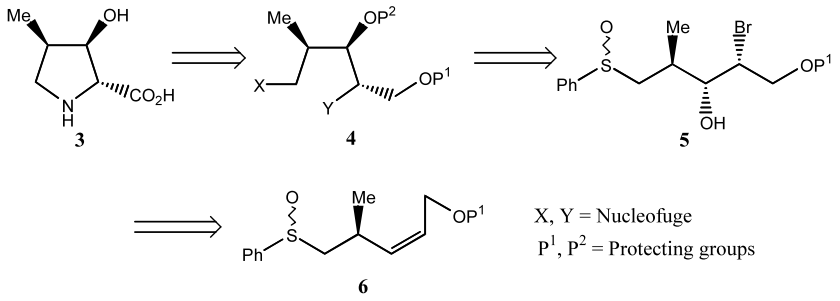


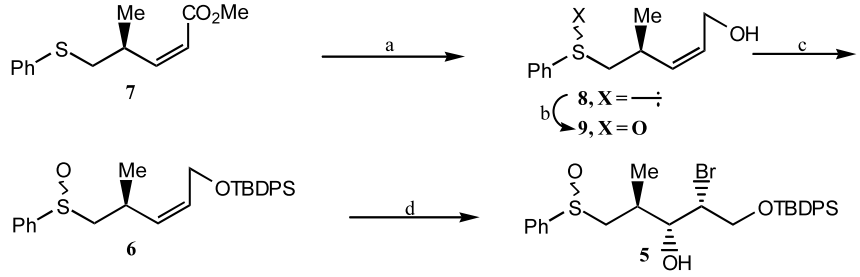
Scheme 1.

N-bromosuccinimide[7] (NBS) in toluene in the presence of water afforded bromohydrin (**5**) (Scheme 2).

The regio- and stereoselectivity of bromohydration can be rationalized by invoking the intermediates **I** and **II**, formed by 5-*exo* nucleophilic attack of the sulfinyl moiety on the olefin, π complexed to the bromonium ion,[8] and subsequent hydrolysis by attack of water at sulfur[9] (Fig. 1).

The required carbon framework was thus assembled highly stereoselectively. The next step in the synthesis called for the transformation of the sulfinyl moiety in **5** into a suitable leaving group. This was achieved as follows. The secondary hydroxy group was protected as a benzoate ester (**10**) by treatment with benzoic acid and DCC. Attempted protection of **5** with benzoyl chloride in the presence of a suitable base afforded a complex mixture of products, probably arising from the reaction of the reagent with the sulfinyl group in a Pummerer type reaction. Subjecting **10** to Pummerer reaction conditions[10] by treatment with excess trifluroacetic anhydride (TFAA) and triethylamine (Et_3N) in acetonitrile as the solvent followed by in situ hydrolysis and reduction of the intermediate (**11**) with saturated aq. $NaHCO_3$ and $NaBH_4$ afforded the primary alcohol (**12**) (Scheme 3). It is pertinent to mention that Pummerer reaction on the substrate wherein the secondary hydroxy group was protected as its acetate, afforded after hydrolysis and reduction, a mixture of products resulting from acetyl migration to the primary hydroxy group.

Tosylation of the primary hydroxy group by treatment with *p*-toluenesulfonyl chloride (Ts-Cl) in the presence of Et_3N yielded **13**. The crucial (4C+N) cyclization proceeded without incident by warming **13** with excess benzylamine in DMF as the solvent to afford pyrrolidine (**14**). Elaboration of **14** to **3** required deprotection of *N*-Bn, silyl groups and oxidation of the resulting primary hydroxy group. Thus hydrogenolysis of **14** by treatment with Pd/C in the presence of $(Boc)_2O$ under



Scheme 2. *Reaction conditions*: (a) AlH_3, Et_2O, 0°C, 2 h, 93%. (b) $NaIO_4$, MeOH, H_2O, rt, 16 h, 95%. (c) TBDPS-Cl, imidazole, DCM, rt, 3 h, 78%. (d) NBS, H_2O, toluene, rt, 4 h, 75%.

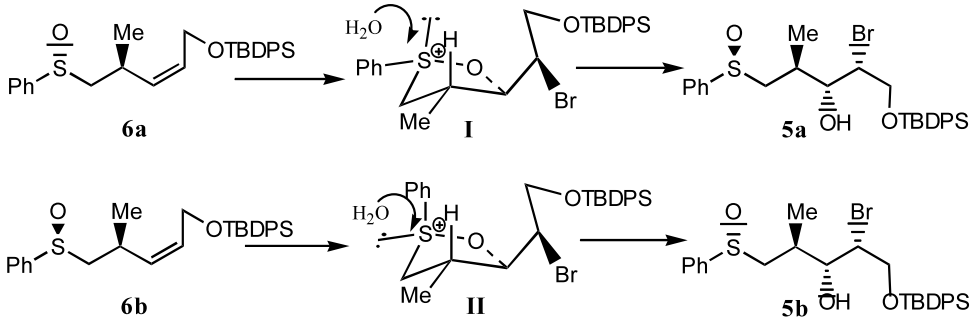
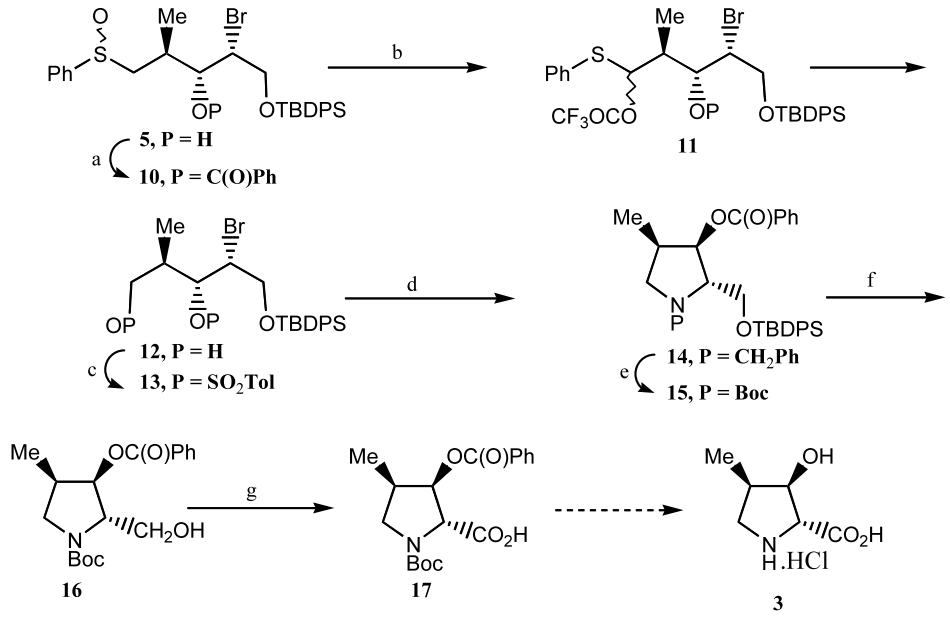


Figure 1.



Scheme 3. *Reaction conditions*: (a) PhCOOH, DCC, DMAP, DCM, rt, 12 h, 90%. (b) TFAA, Et_3N, CH_3CN, rt, $NaBH_4$, $NaHCO_3$, 70%. (c) TsCl, Et_3N, DCM, rt, 12 h, 85%. (d) $PhCH_2NH_2$, DMF, 60°C, 4 h, 70%. (e) H_2, Pd/C, $(Boc)_2O$, rt, 12 h, 90%. (f) CSA, MeOH, DCM, rt, 24 h, 78%. (g) $PhI(OAc)_2$, Tempo, CH_3CN, H_2O, rt, 1 h, 91%.

an atmosphere of hydrogen in methanol as the solvent afforded carbamate (**15**) as a mixture of rotamers. Deprotection of the silyl group was realized by treatment of **15** with catalytic amounts of camphor-10-sulfonic acid (CSA)[11] to afford alcohol (**16**). The primary hydroxy group was oxidized readily with $PhI(OAc)_2$/Tempo[12] to afford the acid (**17**), which was found to be identical (except for the sign of rotation of plane polarized light) to the sample synthesized by Langlois and co-workers,[3] who have further transformed it to HMP. Thus we have completed a formal synthesis of (2*R*,3*R*,4*R*)-HMP. Beginning with the enantiomer of the ester (**7**), (2*S*,3*S*,4*S*)-HMP can be elaborated following the sequence of reactions detailed above.

In conclusion, we have disclosed a practical, efficient and a stereoselective route to (2*R*,3*R*,4*R*)-HMP. The key steps include (a) the regio- and stereoselective elaboration of **5** by intramolecular sulfinyl group participation, (b) a novel (4C+N) cyclization to elaborate the pyrrolidine moiety which would prove very useful to access other members of this class of compounds.

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