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A Formal Synthesis of a Novel Immunosuppressant ISP-1 : Stereo-controlled Pd(O) Catalysed cis-Hydroxyamination of Carbohydrate derived Vinyl Epoxide

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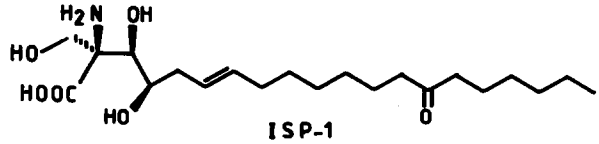
Abstract: Described herein are the results leading to the synthesis of ISP-1 containing an unusal α,α-disubstituted amino acid and whose immunosuppressive activity only has recently been discovered.

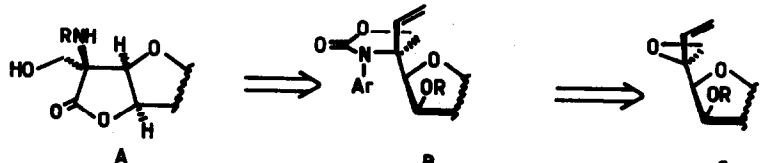
The current level of interest in chiral α,α-disubstituted amino acids has been intensified because they (i) show enzyme inhibitory activities, (ii) influence structures of polypeptides incorporating them and (iii) form part structures of many bioactive natural products[1]. For



ISP-1

instance the novel immunosuppressant ISP-1 (**1**), recently isolated[2] from the culture broth of Isaria sinclairii (Berkeley) sacc. (ATCC No. 24400), contained an unusual α,α-disubstituted amino acid framework. ISP-1 (myriocin or thermozymocidin[3,4]) is an attractive target because the newly discovered immunosuppressive activity was comparable to or slightly higher than clinically used cyclosporin A and secondly the structural features were rather simple as compared to other immunosuppressive agents, cyclosporin A or FK-506. In fact, ISP-1 has been converted into several analogues, many of which are currently undergoing clinical trials[5].

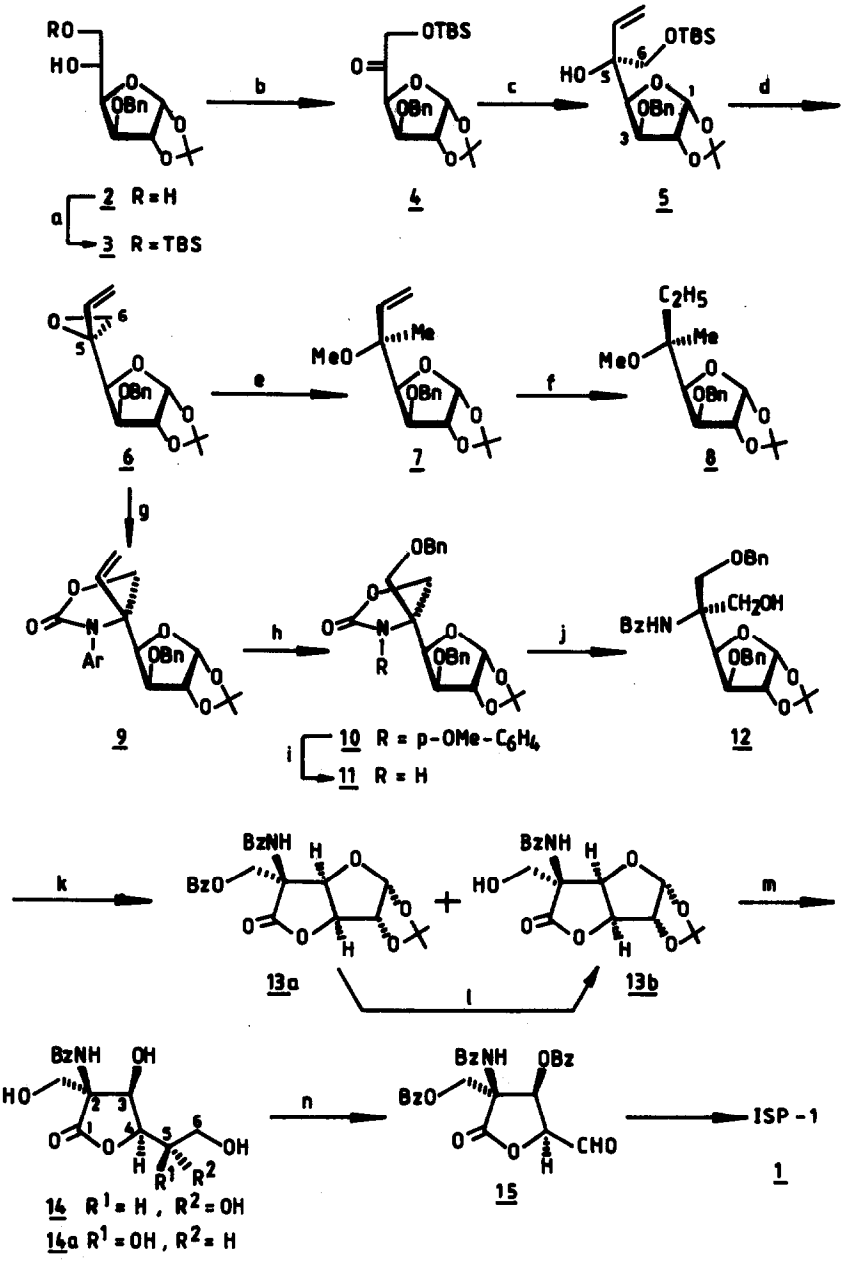
At the methodological front, the critical Strecker type but modified reaction to generate α, α-disubstituted amino nitrile precursors has been employed by earlier workers[6,7], however, the diastereoselectivity was found extremely poor providing almost 1:1 mixture of isomers of the corresponding α,α-disubstituted amino acids. We, therefore, proposed to design an alternate but stereochemically controlled approach (retrosynthesis scheme 1) for the crucial precursor (compound type A) for which we chose carbohydrate as the starting material[8] and relied upon Pd(O) catalysed cis-hydroxyamination reaction of chiral vinyl epoxide. Trost and coworkers[9], with a variety of vinyl epoxides, have exemplified this reaction which occur with high degree of regioselectivity with retention of epoxide configuration. The stereochemical centers at C-3 and C-4 of D-glucose correlated with C-4 and C-3 of the target molecule **1**. However, the off-template stereoselectivity of the cis-hydroxyamination reaction (compound type B)



A B C

Scheme-1

Scheme - 2



(a) TBS-Cl, Imid., DMF, RT, 4h; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°, 2h; c) CH_2=CH-MgBr, THF, RT, 1h; d) (i) Bu_4NF, THF, RT, 2h; ii) PPh_3, DEAD, $C_6H_4CH_3$, Δ, 5h; e) (i) NaI, Bu_3SnH, AIBN (cat), C_6H_6, Δ, 6h; ii) NaH, MeI, THF, RT, 5h; f) (i) Pd-C, H_2, MeOH, 1 atm, 3h; ii) NaH, BnBr, THF, 5h; g) 4-OMe-C_6H_4-NCO, $Pd(PPh_3)_4$, THF, $(CH_3(CH_2)_3CHO)_3P$, RT, 18h; h) i) O_3, CH_2Cl_2, $NaBH_4$; ii) NaH, BnBr, THF, 5h; i) CAN, CH_3CN-H_2O, RT, 6h; j) i) 5N NaOH, THF, Δ, 3-5h; ii) Bz_2O, MeOH, 24h; k) i) $RuCl_3$, $NaIO_4$, H_2O, CCl_4, CH_3CN, RT, 6h; ii) CH_2N_2, EtOEt, 1h; iii) Pd-C, H_2, MeOH, 35 psi, 24h; l) NH_3, MeOH, 30 min., m) i) CH_3COOH, H_2O, 50°, 5h; ii) $NaCNBH_3$, THF, RT, 2h; n) Ref. 7.

on carbohydrate derived vinyl epoxide (interestingly containing many chiral centers, compound type C) would require special attention.

Compound **2** (readily obtainable[10] from D-glucose) was mono-silylated (TBS-Cl, Imid. DMF) to give **3** which by Swern oxidation (DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 -78°) was transformed into the 5-ulose derivative (**4**). Treatment of **4** with vinylmagnesium bromide in THF gave **5**[14] as an exclusive product (80%). The structure and the configuration at C-5 were confirmed by the following sequence of transformations leading to a known product[11]. For example, **5** was subjected to desilylation (Bu_4NF, THF) and then to epoxidation reaction under the Mitsunobu conditions[12] (DEAD, TPP, $C_6H_4CH_3$, δ) to provide **6**. When **6** was heated under reflux with NaI, tributyltin hydride in refluxing benzene containing cat. AIBN[13], the 6-deoxy product was isolated which on methylation (NaH, MeI, THF) gave **7**. Its subsequent hydrogenation (Pd-C,H_2, MeOH) and re-benzylation (NaH, BnBr,THF) afforded the known compound **8** ($[\alpha]_D$ -64°, lit.[11] $[\alpha]_D$ -68°). Having established, during the above process, the absolute stereochemistry of the vinyl epoxide (**6**), we then considered the cis-hydroxyamination step. 4-Methoxyphenylisocyanate was the reagent of choice due to readily removable 4-methoxyphenyl group. Treatment of **6** with 4-methoxyphenylisocyanate in the presence of a catalytic amount of Pd $(PPh_3)_4$ and triisopropylphosphite in THF gave a single oxazolidinone derivative **9** (76%). Although, the ^{1}H-NMR spectrum revealed the gross structure of the product, the absolute stereochemical assignments were based on single crystal X-ray diffraction studies (Fig.A).

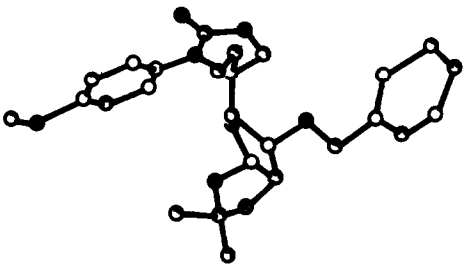


Figure- A (9)

Compound **9** was subjected to successive ozonolysis (O_3, CH_2Cl_2) in situ reduction ($NaBH_4$) and benzylation (NaH, BnBr, THF). From the expected product **10**, 4-methoxyphenyl substituent was cleaved (CAN, CH_3CN-H_2O), to obtain **11**. Hydrolysis of the oxazolidinone ring with an alkali (5N NaOH, THF, δ) then gave the amino alcohol derivative which was selectively N-benzoylated [$(Bz)_2O$, MeOH] to provide **12**.

For the forthcoming conversion of CH_2OH → COOMe, **12** was oxidised ($RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O) and esterified (CH_2N_2, EtOEt) to afford two products as judged by TLC. However, the mixture as such was hydrogenolysed (Pd-C,H_2, MeOH) and then chromatographed to provide **13a** and **13b** (1:3) (85%). Their structures were illustrated by the ^{1}H-NMR spectra. The resonances due to methylene protons were clearly apparent in both spectra of **13a** and **13b** as a AB quartet, but whereas the positions of all other ring proton resonances were comparable, that due to the methylene protons showed an upfield shift of 0.79 ppm in the benzoylated product (**13a**). The isolation of **13a** indicated that at Ru-oxidation stage, the primary O-benzylic group also underwent selective oxidation to generate O-benzoate, while the secondary O-benzyl remained uneffected. However, de-O-benzoylation of **13a** (NH_3, MeOH) furnished **13b**. Cleavage of the isopropylidene group (CH_3COOH, H_2O, 50°) and reduction ($NaCNBH_3$, THF) provided **14**. All the stereochemical centers in **14** correlated with those present in the key intermediate **14a** except for the chiral center at C-5 which is anyway destroyed in the subsequent steps

to produce the aldehyde 15[7]. Compound 15 has already been converted into myriocin (ISP-1)[7].

This communication describes the first stereocontrolled approach towards the biologically and medicinally valuable immunosuppressant ISP-1. We are now contemplating the applications of this approach to other α,β-disubstituted amino acids of biological significances.

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14. Physical data of some selected compounds:
    Compound **5**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.02 (s, 6H, Me_2Si), 0.87 (s, 9H, $(CH_3)_3$ CSi), 1.34, 1.48 (2s, 6H, Me_2C), 3.44 (d, 1H, J 8.0 Hz, H-6a), 3.59 (d, 1H, J 8.0 Hz, H-6b), 4.12 (d, 1H, J 3.4 Hz, H-3), 4.29 (d, 1H, J 3.4, H-4), 4.48, 4.68 (ABq, 2H, $PhCH_2$), 4.59 (d, 1H, J 4.2 Hz, H-2), 5.17 (dd, 1H, J 1.0, 10.7 Hz, 1/2 CH_2= [cis], 5.44 (dd, 1H, J 1.0, 17.0 Hz, 1/2 CH_2= [trans]), 5.97 (d, 1H, J 4.2 Hz, H-1), 6.0 (m, 1H, CH=), 7.30 (s, 5H, Ph). $[\alpha]_D$ -25° (c 1.3, $CHCl_3$).
    Compound **6**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.34-1.50 (2s, 6H, Me_2C), 2.74 (d, 1H, J 8.0 Hz, H-6a), 3.18 (d, 1H, J 8.0 Hz, H-6b), 4.08 (d, 1H, J 3.6 Hz, H-3), 4.32 (d, 1H, J 3.6 Hz, H-4), 4.58 (ABq, 2H, $PhCH_2$), 4.64 (d, 1H, J 4.0 Hz, H-2), 5.18 (dd, 1H, J 1.0, 12.0 Hz, 1/2 CH_2= [cis]), 5.38 (dd, 1H, J 1.0, 18.0 Hz, 1/2 CH_2= [trans]), 5.94 (d, 1H, J 4.0 Hz, H-1), 6.05 (m, 1H, CH=), 7.30 (m, 5H, Ph). $[\alpha]_D$ -60° (c 1.1, $CHCl_3$).
    Compound **7**: ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.46, 1.50 (3s, 9H, Me_2C+CH_2), 3.20 (s, 3H, OMe), 3.88 (d, 1H, J 3.6 Hz, H-3), 4.06 (d, 1H, J 3.6 Hz, H-4), 4.44, 4.62 (ABq, 2H, $PhCH_2$), 4.54 (d, 1H, J 4.0 Hz, H-2), 5.15-5.41 (m, 2H, CH=), 5.84 (dd, 1H, J 12.0, 18.0 Hz, CH=), 5.96 (d, 1H, J 4.0 Hz, H-1), 7.30 (s, 5H, Ph).
    Compound **9**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30, 1.35 (2s, 6H, Me_2C), 3.76 (bs, 4H, OMe+H-6a), 4.14 (d, 1H, J 3.5 Hz, H-3), 4.26 (d, 1H, J 7.0 Hz, H-6b), 4.30 (d, 1H, J 3.5 Hz, H-4), 4.52, 4.73 (ABq, 2H, $PhCH_2$), 4.54 (d, 1H, J 4.2 Hz, H-2), 5.30 (dd, 1H, J 11.9, 17.8 Hz, CH_2=), 5.72 (dd, 1H, J 11.9, 17.8 Hz), 6.00 (d, 1H, J 4.2 Hz, H-1), 6.83 (d, 2H, Ar), 7.3 (m, 7H, Ar). Mass spectrum : m/z 467 (M^+). [ ]$_D$ -64° (c 1.3, $CHCl_3$).
    Compound **13b**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.43, 1.52 (2s, 6H, Me_2C), 4.06 (ABq, 2H, J 12.7 Hz, CH_2), 4.88 (d, 1H, J 4.0 Hz, H-5), 5.09 (d, 1H, J 3.2 Hz, H-3), 5.31 (d, 1H, J 3.2 Hz, H-4), 5.95 (d, 1H, J 4.0 Hz, H-6), 6.70 (s, 1H, NH), 7.4-7.9 (m, 5H, Ph). $[\alpha]_D$ +19° (c 0.3, $CHCl_3$).

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