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Diversity oriented concise asymmetric synthesis of azasugars: a facile access to L-2,3-*trans*-3,4-*cis*-dihydroxyproline and (3*S*,5*S*)-3,4,5-trihydroxypiperidine

Vikas S. Gajare [a,c], Sandip R. Khobare [a], Rajender Datrika [a], K. Srinivas Reddy [a], Nagaraju Rajana [a], Sarvesh Kumar [b], B. Venkateswara Rao [c], U. K. Syam Kumar [b,*]

[a] Technology Development Center, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Miyapur, Telangana 500049, India
[b] Integrated Product Development Organization, Dr. Reddy's Laboratories Ltd, Innovation Plaza, Bachupally, Telangana 500072, India
[c] AU College of Engineering (A), Andhra University, Visakhapatanum 530003, India

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ABSTRACT

Diversity oriented concise asymmetric syntheses of L-2,3-*trans*-3,4-*cis*-dihydroxyproline and (3*S*,5*S*)-3,4,5-trihydroxypiperidine have been developed from (*R*)-glycidol. The key step of the synthesis is Sharpless asymmetric dihydroxylation on enantiomerically pure TBDMS protected allylic alcohol **14** which generates the triol intermediate **15** in excellent *de*. The (2*R*,3*R*,4*S*)-2,3-dihydroxypentanoate derivative **15** was subsequently converted to natural pyrrolidine azasugar **1** and non-natural piperidine azasugar **4** under cascade reaction conditions in good yields.

Substituted pyrrolidine and piperidine azasugars are important class of biologically active molecules as many of these compounds exhibit promising chemotherapeutic potential in the treatment of various diseases such as viral infections, cancer, AIDS, and diabetes.[1] Nojirimycin[2a] (**3**) and deoxynojirimycin[2b] (**3a**) have been found to be potent glycosidase inhibitors (Fig. 1). Minor structural or functional modifications on these carbohydrate mimetics can impart remarkable changes to their potency and specificity of inhibition.[3] Polyhydroxylated pyrrolidines and piperidines are found to be potent anti-HIV,[4] anti-neoplastic and anticancer agents.[5] They are also present in active molecules for the treatment of diabetes and viral infections.[6] Due to the remarkable biological importance of these classes of azasugars, their concise, efficient, and enantioselective synthesis are highly desirable.

On the onset of our studies, the motive was to develop efficient routes for the synthesis of natural product 2,3-*trans*-3,4-*cis*-dihydroxy proline (DHP) **1** and (3*S*,5*S*)-3,4,5-trihydroxy piperidine **4**. The natural product **1** was isolated from the marine mussel *Mytilus edulis* and it was structurally identified as a constituent of the sixth residue in the repeating decapeptide sequence of the adhesive protein Mefp1.[7] Fleet and Son had demonstrated the synthesis of 2,3-*trans*-3,4-*cis*-dihydroxy proline (**1**) from D-gluconolactone in 1988 before its identification from natural sources.[8] Subsequently, different synthetic approaches are reported in the literature for the synthesis of **1**. Most of these synthetic protocols for the deceptively simple looking azasugars relay upon carbohydrate or chiral aminoacids as starting material for achieving stereochemical requirement of polyhydroxy frame work.[9] Azasugars **5**–**7** (Fig. 1) had been isolated from *Eupatorium fortunei* TURZ by Kusano and co-workers.[10] The plant extract of *Eupatorium fortunei* TURZ was traditionally used in folk medicines as diuretic, antipyretic, emmanagogue and also as antidiabetic agent.

Results and discussion

Ganem and co-workers, reported the synthesis of 3,4,5-trihydroxy piperidines **5**, **7,** and **8** starting from D-hexose before their isolation from natural sources.[11] Other synthetic approaches for these chirally pure azasugars reportedly use Grubbs metathesis[12] and photo-induced electron transfer reaction[13] as key steps. As a part of our efforts to develop new methodologies for the synthesis of biologically active natural products,[14] herein we disclose a diversity oriented and concise asymmetric approach to access

* Corresponding author. Fax: +91 4023045439/5438.
E-mail address: syam_kmr@yahoo.com (U.K. Syam Kumar).

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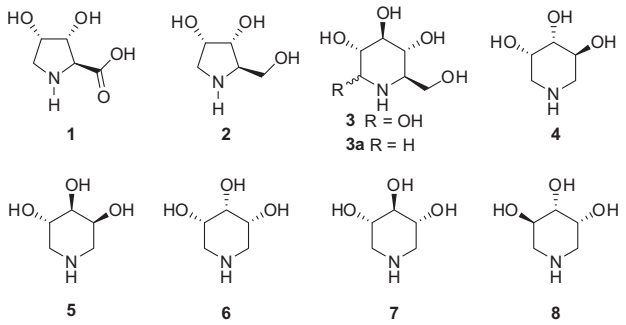
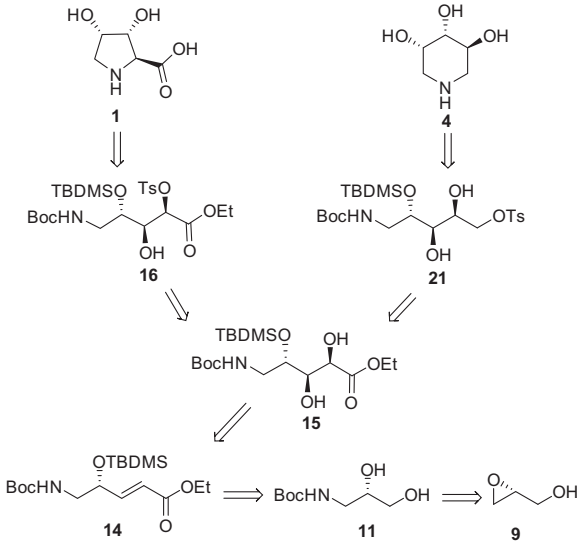


Figure 1.

natural product 2,3-*trans*-3,4-*cis*-dihydroxy proline **1** and non-natural product (3*S*,5*S*)-3,4,5-trihydroxy piperidine **4** with high diastereoselectivity. Our synthetic design was surmised to access both the pyrrolidine and piperidine based natural azasugars **1** and **4** from simple and commercially accessible *R*-glycidol chiral entity.

The retrosynthetic design for the stereoselective synthesis of **1** and **4** is described in Scheme 1. 2,3-*trans*-3,4-*cis*-Dihydroxyproline (**1**) could be obtained from *N*-Boc amino ester intermediate **16** by the global deprotection of *N*-Boc and *O*-TBDMS groups followed by the base induced cyclization. Intermediate **16** could be obtained by the selective tosylation of active hydroxyl group of diol **15**, which in turn could be accessed from allyl hydroxyl ester intermediate **14** under Sharpless asymmetric dihydroxylation conditions. The *trans* α,β-unsaturated ester **14** could be obtained by the selective oxidation of primary hydroxyl group followed by Wittig olefination on aminodiol intermediate **11**. The aminodiol intermediate **11** in turn could be synthesized from *R*-glycidol by following the literature report.[15] On the other hand, the azasugar (3*S*,5*S*)-3,4,5-trihydroxy piperidine (**4**) could be synthesized from the aminotetrol derivative **21**. The reduction of ester functionality in **15** followed by the selective tosylation of the primary hydroxyl group could afford the aminotetrol derivative **21**.

The synthesis of natural product 2,3-*trans*-3,4-*cis*-dihydroxy proline **1** and (3*S*,5*S*)-3,4,5-trihydroxy piperidine **4** was initiated with commercially available enantiomerically pure (*R*)-glycidol (**9**). Exposure of glycidol **9** to aqueous ammonia at 0 °C for 24 h



Scheme 1. Retro synthetic analysis.

followed by the Boc protection in methanol in the presence of catalytic amount of TEA (0.1 equiv) afforded *N*-Boc amino diol **11** as a single enantiomer. The selective oxidation of primary hydroxyl group in **11** to the corresponding aldehyde **12** by keeping the unprotected secondary alcohol intact was attempted next. Various oxidation conditions including TCCA/TEMPO,[16] NaOCl/TEMPO,[17] NCS/TEMPO[18] etc., were screened. Good yield along with high site selectivity was observed when the oxidation was carried out with TEMPO/TCCA in ethyl acetate. The aldehyde **12** was found to be unstable, hence we decided to use it directly for Wittig olefination reaction without further purification. Thus, the exposure of **12** to Wittig olefination reaction with ethyl-2-(triphenylphosphoranylidene)acetate in DCM furnished the required product after column chromatographic purification in 49% isolated yield. Wittig olefination reaction furnished *trans*-alkene as the major product which was confirmed by coupling constant value in ^{1}H NMR spectrum (J = 15.6 Hz). The minor product *cis* olefin presumably underwent intramolecular cyclization to the corresponding furanone either during the reaction or during the column chromatography, however, the furanone couldn't be characterized, as it was heavily contaminated with triphenylphospine oxide.[19] The attempted Sharpless asymmetric dihydroxylation reaction on allylic hydroxyl ester intermediate **13** with AD-mix-α did not afford the required product. Reasoning that the chelation of unprotected allylic hydroxyl group with 'Os reactive species' during the course of dihydroxylation might be the possible cause (Fig. 2) for the failure of Sharpless asymmetric hydroxylation reaction,[20] the free hydroxyl group in **13** was protected as TBDMS ether. The TBDMS protected intermediate **14** was subsequently subjected to Sharpless asymmetric dihydroxylation reaction[21] using AD-mix-α to furnish the required product **15** in 65% yield as a single diastereomer (Scheme 2). The structure of **15** was established by NOESY and COSY NMR studies, and the stereochemical configuration is assigned based on the literature precedence on similar substrates obtained via Sharpless asymmetric dihydroxylation reaction.[22] The bulky TBDMS protected hydroxyl group plays critical role for the facial selectivity during the Sharpless asymmetric dihydroxylation reaction (Fig. 2) as it controls the rotational isomer population.[23]

Dihydroxy intermediate **15** was subsequently subjected to selective tosylation of the secondary alcohol α to the ester in the presence of TsCl/TEA in DCM solvent. The reaction was sluggish at 0–5 °C and the desired product **16** was formed only in 30% yield even after prolonged maintenance of the reaction mixture for about 72 h. However, when the reaction was conducted at 25–30 °C, better conversion was observed and **16** was isolated in 63% yield along with around 20% of unreacted starting material. Under these reaction conditions, tosylation was found to be highly regioselective, probably due to proximity of C2 hydroxyl with ester group which increase its acidity and thus favouring the selective monotosylation.[24] Also the C2 hydroxyl group is far away from the bulky OTBDMS, which also make the tosyl protection on C2 highly regioselective with respect to C3. The global deprotection of *N*-Boc and *O*-TBDMS groups in hydroxyl intermediate **16** was performed with a solution of HCl in 1,4-dioxane (4 M) at ambient temperature. Under these acidic conditions, the global deprotected compound **17** underwent in situ lactonisation to afford **18**. Being an HCl salt, the lactone **18** was found to be highly hygroscopic and attempted isolation of this intermediate **18** was not successful. Therefore, **18** was subsequently subjected to barium hydroxide treatment which resulted in a cascade reaction involving the neutralization of HCl salt, ring opening of the lactone, and further heteroannulation to the required natural product 2,3-*trans*-3,4-*cis*-dihydroxy proline **1** as a barium salt.[25] The pH of the reaction mixture was adjusted to 5 with acetic acid and the resulting reaction mixture was purified over IR 120 acidic resin to afford **1**[26] as

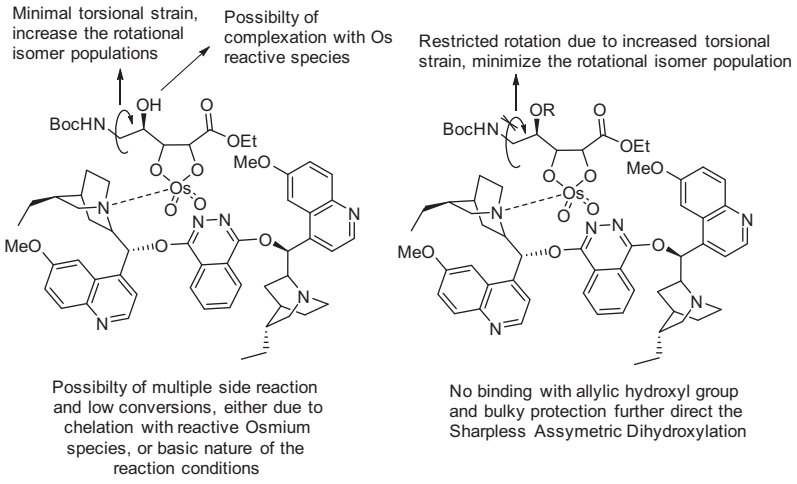
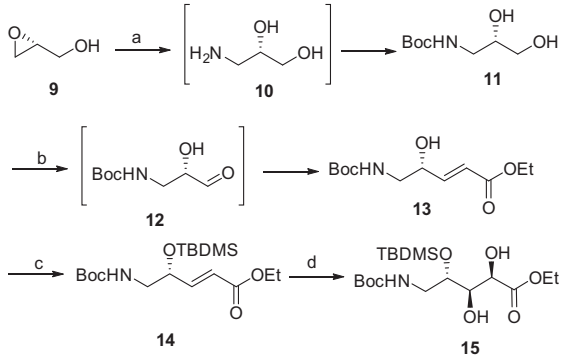
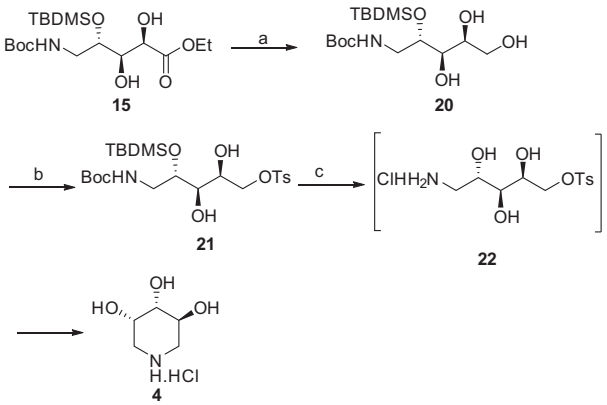


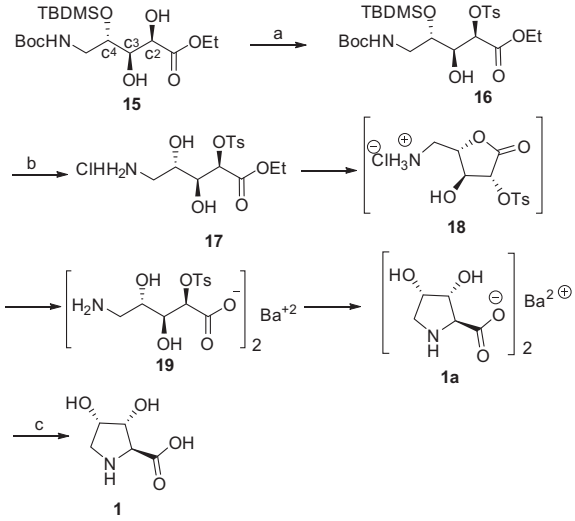
Figure 2.



Scheme 2. (a) (i) aq ammonia, 0 °C, 24 h; (ii) $(Boc)_2O$, MeOH, TEA (cat.), rt, 71% (two step); (b) (i) TCCA/TEMPO, ethyl acetate, 5 °C; (ii) Ph_3P = CHCOOEt, DCM, 30 °C, 3 h, 49% (two steps); (c) TBDMSCl, imidazole, DCM, rt, 16 h, 91%; (d) $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, OsO_4, AD mix α, 0 °C to RT, 65%.



Scheme 4. (a) $NaBH_4$, THF/MeOH, 0 °C to rt, 2 h, 85%; (b) TsCl/NMI, DCM, 0 °C, 3 h, 71%; (c) (i) HCl in EtOAc, rt 3 h; (ii) DIPEA, water, rt, 30 h; (iii) 6 N HCl in methanol, 73%.



Scheme 3. (a) TsCl, TEA, DCM, 0 °C to RT, 16 h, 63%; (b) (i) 1,4-dioxane:HCl, rt, 2 h (ii) 0.1 N $Ba(OH)_2$, (pH = 9), rt, 3 h, (c) IR 120 resin, 77%.

white solid in 77% overall yield (Scheme 3). The spectral data of the natural product 2,3-*trans*-3,4-*cis*-dihydroxy proline **1** is in agreement with the literature reported values. $[\alpha]_D^{22}$ +7.99° (*c* 0.3, H_2O); Mp 244.8 °C, [Lit.[8] $[\alpha]_D^{20}$ +7.5° (*c* 0.16, H_2O), Mp 247 °C]. The overall yield of the synthesis of 2,3-*trans*-3,4-*cis*-dihydroxy proline **1** is 16.5% starting from enantiomerically pure (*R*)-glycidol (**9**).

After the successful synthesis of the natural product **1**, we focused our attention toward the enantio pure synthesis of (3*S*,5*S*)-3,4,5-trihydroxy piperidine **4** (pure single diastereomer) (Scheme 4). Thus ethyl-2,3-dihydroxypentanoate derivative **15** was subjected to ester reduction using sodium borohydride in a mixture of methanol and THF to provide *tert*-butyl ((2*S*,3*R*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-3,4,5-trihydroxypentyl)carbamate **20** in 85% isolated yield. The regioselective tosylation of the primary hydroxyl group in the presence of secondary alcohol was accomplished in 71% isolated yield using TsCl in the presence of *N*-methyl imidazole as a mild base.[27] No di-tosylation was observed under these reaction conditions. The monotosyl intermediate **21** was found to be less stable and it decomposed rapidly on heating. However, we were successful in the isolation and characterization of monotosyl intermediate **21**. In the next sequence of reaction for the synthesis of (3*S*,5*S*)-3,4,5-trihydroxy piperidine **4**, the global deprotection of *N*-Boc and *O*-TBDMS groups in **21** was carried out with a solution of hydrochloric acid in ethyl acetate to yield (2*S*,3*S*,4*S*)-5-amino-2,3,4-trihydroxypentyl-4-methylbenzenesulfonate **22** as a highly hygroscopic hydrochloride salt. Subsequent neutralization of **22** was expected to result in

(3*S*,5*S*)-3,4,5-trihydroxy piperidine **4**[28] in diastereomerically pure form via an intramolecular S_N2 process. Different base and solvent combinations, for example, $CaCO_3$ in methanol, TEA in acetonitrile, *N*-methyl morpholine in toluene, etc., were screened for the cyclization of **22**. Under these conditions, the reaction was found to be very sluggish at room temperature and a substantial amount of unreacted starting material was observed even after prolonged reaction time. On the contrary, a complex mixture of products was observed at higher reaction temperatures. Finally, the use of Hunig's base (*N*,*N*-diisopropylethylamine) in water at ambient temperature resulted in complete consumption of the starting material. The crude (3*S*,5*S*)-3,4,5-trihydroxy piperidine **4** was purified on acidic IR 120 resin to afford the enantiopure (3*S*,5*S*)-3,4,5-trihydroxy piperidine as a free base, which was subsequently converted to hydrochloride salt **4** by using 6 N HCl in methanol in 73% yield starting from **21** (Scheme 4). The spectral data of our (3*S*,5*S*)-3,4,5-trihydroxy piperidine are identical to the literature reported values. $[\alpha]_D^{27}$ +15.5° (*c* 0.3, MeOH): Mp 191.1 °C [Lit.[11] $[\alpha]_D$ +16° (*c* 0.5, MeOH), Mp 191–192 °C].

In conclusion, a versatile asymmetric strategy for the construction of L-2,3-*trans*-3,4-*cis*-dihydroxyproline **1** and (3*S*,5*S*)-3,4,5-trihydroxypiperidine (pure single diastereomer) **4** has been developed from chirally pure glycidol for the first time in the literature. The synthesis involves multiple cascade reactions, site selective oxidation and regioselective protection as well as intramolecular heteroannulation. It is quite obvious that other densely functionalized piperidine and pyrrolidine azasugars can be synthesized by following synthetic methodology described here with excellent stereo chemical controls.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.013.

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26. *Synthesis of (2S,3R,4S)-3,4-dihydroxypyrrolidine-2-carboxylic acid* (**1**): A solution of 16 (300 mg, 0.534 mmol) in 1,4-dioxane HCl (3 mL, 4 molar solution) was stirred for 3 h at ambient temperature. After completion of the reaction, solvents were evaporated under vacuum and the residue was diluted with water (9.0 mL). Reaction mixture was maintained at pH 9.0 for 4 h by drop wise addition of 0.1 N $Ba(OH)_2$ solution. The reaction mass was acidified with acetic acid to pH ~ 5 and purified with acidic resin IR 120 (H^+). Product was eluted in 5% aqueous ammonia. Product fraction was evaporated to get solid which was further purified with ethanol to afford 60.5 mg (77% yield) of the desired product (1). ^{1}H NMR (400 MHz, D_2O): δ ppm 3.28 (dd, *J* = 12.3, 3.9 Hz, C5HA, 1H), 3.52 (dd, *J* = 12.3, 4.9 Hz, C5HB, 1H), 3.97 (d, *J* = 4.9 Hz, C2H, 1H), 4.32–4.37 (m, C3H and C4H, 2H); ^{13}C NMR (100 MHz, D_2O, trimethylsilylpropionic acid sodium salt used as internal reference): δ ppm 51.2, 67.1, 72.8, 76.9, 174.9. IR (KBr) cm^{-1}: 3402, 3245, 2714, 2567, 1650, 1613, 1438, 1344, 1255, 1137. HRMS (ESI): Calcd for $C_5H_{10}NO_4$ $(M+H)^+$ 148.0610, found 148.0614. $[\alpha]_D^{22}$ +7.99° (*c* 0.3, H_2O), Mp 244.8 °C. [lit[8]: $[\alpha]_D^{20}$ +7.5° (*c* 0.16, H_2O), Mp 247 °C].
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28. *Synthesis of (3S,5S)-piperidine-3,4,5-triol hydrochloride* (**4**): A solution of **21** (500 mg, 0.96 mmol) in ethyl acetate containing HCl (10 mL) was stirred at ambient temperature for 3 h. Solvent was evaporated under vacuum and the residue was diluted with water (5 ml). *N*,*N*-Diisopropyl ethyl amine (621 mg, 4.82 mmol) was added to the reaction mixture and stirred for 30 h at ambient temperature. Solvent was evaporated under vacuum and the residue was diluted with water (5 mL). The mixture was acidified with acetic acid to pH ~ 5 and purified using acidic resin IR 125 (H^+). Product eluted in 5% aqueous ammonia. Product fraction was evaporated under vacuum to get free amine. The free amine was further diluted with methanol and treated with 6 M HCl,

stirred, and concentrated under vacuum to obtain the hydrochloride salt, which was further purified with ethanol to afford 120 mg (73% yield) of the desired product. ^{1}H NMR (400 MHz, D_2O): δ ppm 2.92 (dd, J = 12.7, 8.3 Hz, 1H [H2ax]), 3.17–3.20 (m, 1H, [H6ax]), 3.25 (dd, J = 13.2, 5.9 Hz, 1H, [H6eq]), 3.37 (dd, J = 12.7, 2.4 Hz, 1H [H2eq]), 3.75 (dt, J = 7.8, 2.4, 1H, [H4]), 4.05–4.10 (m, 1H [H3]), 4.21–4.23 (m, 1H, [H5]); ^{13}C NMR (100 MHz, D_2O): δ ppm 45.5, 46.0, 64.7, 65.0, 70.8. IR (KBr) cm^{-1}: 3345, 3298, 3081, 2922, 2903, 2855, 1610, 1440, 1406, 1368. HRMS (ESI): Calcd for $C_5H_{12}NO_3$ $(M+H)^+$ 134.0817, found 134.0811. $[\alpha]_D^{27}$ +15.5° (c 0.3, MeOH), Mp 191.1 °C. [lit[11] $[\alpha]_D$ +16° (c 0.5, MeOH), Mp 191–192 °C].