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Norbornyl Route to Cyclopentitols: Synthesis of Trehazolamine Analogues and the Purported Structure of Salpantiol

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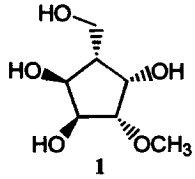
Abstract: A new approach to aminocyclopentitols, leading to a synthesis of trehazolamine analogues is delineated. Synthetic studies on the cyclopentitol natural product salpantiol indicates that its assigned structure is incorrect.

In recent years, molecular entities having cyclopentitol (polyhydroxylated cyclopentanes) or aminocyclopentitol core structures have emerged as a versatile and powerful group of glycosidase inhibitors.[1] An interesting aspect of this family of compounds is the stereochemical and functional group diversity present in them despite the fact that they share quite similar mechanisms of action. This structural variety among cyclopentitols is indicated by the natural products salpantiol **1**,[2a,b] mannostatin **2**,[2c] neoplanocin **3**[2d] and trehazolamine **4**, the aglycon of the trehalase inhibitor trehazolin **5**.[2e] In addition, many synthetic aminocyclopentitols, like Merrel Dow's cyclopentylamine **6**,[1b] have been found to exhibit specific inhibitory activity against glycosidases. The syntheses of cyclopentitols and aminocyclopentitols is an active research area; several syntheses of **2-6** have been reported during the past decade and efforts towards newer analogues are ongoing endeavours.[1] On the other hand, salpantiol, a cyclopentitol isolated from the flowers of *Salpianthus arenarius* (known as 'catarinita' in Mexico and used in folk medicine for several disorders),[2a,b] assigned structure **1**, has remained in obscurity and not received the attention of synthetic chemists despite its projected biological activity.



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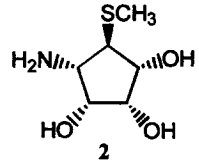

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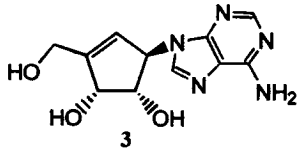

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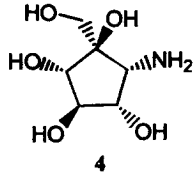

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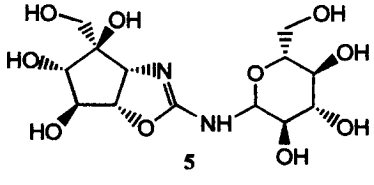

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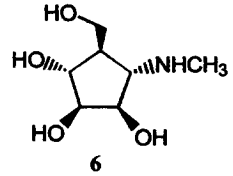

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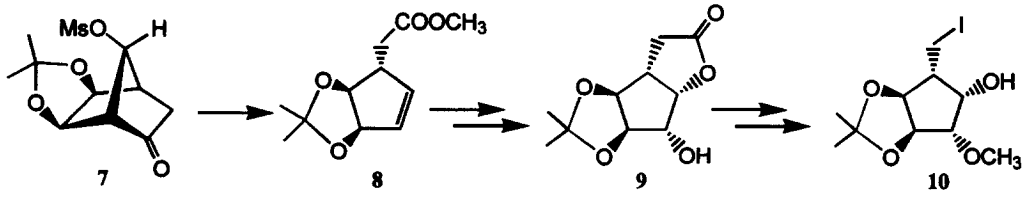
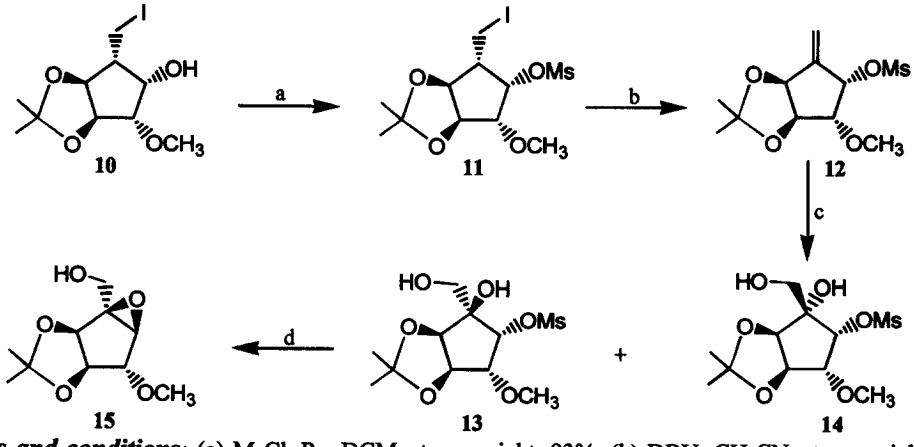
Recently, we devised a new fragmentation protocol of the norbornyl system leading to **10** from the readily accessible norbornyl derivative **7** *via* the intermediates **8** and **9**, Scheme 1.[3] Functionally embellished and stereochemically secured **10** appeared well poised for elaboration to salpantiol **1** and other related cyclopentitols. Herein, we report the synthesis of **1** and find its spectral characteristics to be markedly different from those reported for the natural product salpantiol in the literature.[2a,b] We also report the synthesis of some new aminocyclopentitols related to trehazolamine **4** from **10**.

Scheme 1



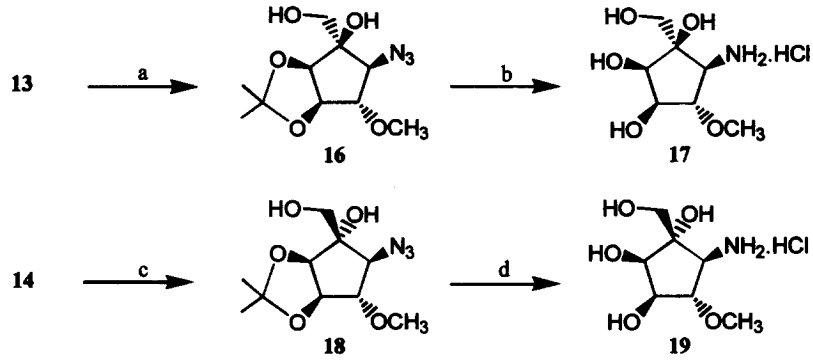
For elaboration to aminocyclopentitol structures, the free hydroxyl group in **10** was activated as its mesylate **11**. On exposure to base, **11** readily underwent elimination to the required exocyclic methylene compound **12**, which was to be the key precursor for the generation of the 1,2-diol functionality present in trehazolamine **4** and related compounds. Catalytic dihydroxylation of **12** with OsO_4 furnished a readily separable mixture (55:45) of diastereomeric diols **13**[4] and **14**.[4] The stereochemistry of the major product **13** was secured through the facile formation of epoxide **15** on treatment with DBU through an intramolecular displacement of the mesylate, Scheme 2. Similar treatment of the diol **14** with DBU did not furnish an epoxide. Introduction of the amino group in to **13** and **14** was achieved through an azidation-reduction sequence. Thus, displacement of the mesylate group in **13** with sodium azide furnished the azido compound **16**, which was reduced to the corresponding amine; deprotection of the acetonide group with dil. HCl led directly to the amine hydrochloride **17**.[4] An identical sequence emanating from **14** led to the salt **19**[4] *via* the intermediate azido compound **18**, Scheme 3. Both, **17** and **19** represent hitherto unknown stereochemical dispositions among aminocyclopentitols and are new analogues of trehazolamine.

Scheme 2



Reagents and conditions: (a) MsCl, Py, DCM, rt, overnight, 93%; (b) DBU, CH_3CN, rt, overnight, 90%; (c) OsO_4, NMMO, Me_2CO:H_2O (4:1), 96h, 84% ; (d) DBU, DCM, 0°C, 2h, 96%.

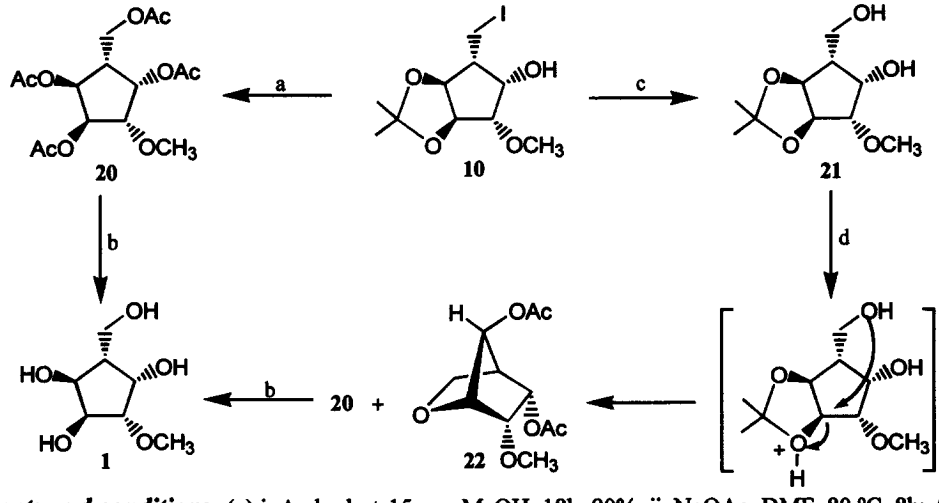
Scheme 3



Reagents and conditions: (a) NaN_3, DMF:HMPA (1:1), 110 °C, 10h, 89%; (b) H_2, Lindlar's catalyst, EtOH, 2h; HCl (5%), Ether:H_2O (2:8), 36h, ~95%; (c) same as (a), 96%; (d) same as (b), 90%

Attention was next directed towards functional group adjustments in **10**, as the stereochemical disposition of substituents was ideally suited towards elaboration to the natural product salpantiol **1**. Acetonide deprotection of **10** to a trihydroxy compound, followed by acetolysis and peracetylation led to the tetra-acetate **20**, whose spectral characteristics (^1H and ^{13}C NMR, including ^1H-^1H COSY and DEPT) were fully consonant with its structure.[5] However, these data were not in agreement with the limited data reported for the tetraacetate derived from the natural product **1**. Tetraacetate **20** was hydrolysed to furnish **1**, but once again the ^1H and ^{13}C NMR data of **1** and that of the natural product were at variance.[5] There are several inconsistencies in the spectral data reported for the natural product and in the light of our synthesis of **1**, the structure of salpantiol needs reinvestigation. Tetraacetate **20** was also accessed from **10** *via* hydrolysis to **21**, acetonide deprotection and acetylation steps.

Scheme 4



Reagents and conditions: (a) i. Amberlyst-15, aq. MeOH, 18h, 90%; ii. NaOAc, DMF, 80 °C, 8h; Ac_2O, Py, overnight, 60% for two steps; (b) NH_3, MeOH, 12h, ~100%; (c) Na_2CO_3, aq. MeOH, reflux, 84%; (d) Amberlyst-15, DCM, rt, 8h, Ac_2O, Py, overnight, 70% for two steps

However, in this case a 1:1 mixture of the desired **20** and a diacetate, tentatively formulated as **22**, formed through intramolecular displacement in **21** during the acid catalysed deprotection step, was obtained, Scheme 4. Formation of **22** is an interesting observation as it provides entry into conformationally restricted bicyclic cyclopentitol analogues.

In short, we have outlined a new route to aminocyclopentitols which is flexible enough to provide entry into many analogues. We have also achieved a synthesis of structure **1** and shown it to be different from the natural product salpantiol, which necessitates the revision of its structure.

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[2] (a) Perez-Gutierrez, R. M.; Perez-Gutierrez, M. S. *Pharm. Acta. Helv.* **1992**, *67*, 156. (b) Salpantiol is among few cyclopentitols that find mention in the '*Dictionary of Organic Compounds*'; Chapman & Hall; 6th ed. Vol 4, 1996: H-02866, pp.3701. (c) Aoyagi, T.; Yamamoto, T.; Kojiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1989**, *42*, 883. (d) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359. (e) Ando, O.; Satake, H.; Itoi, K.; Sato, A.; Nakajima, M.; Takahashi, S.; Haruyama, H.; Ohkuma, Y.; Kinoshita, T.; Enokita, R. *J. Antibiot.* **1991**, *44*, 1165.

[3] Mehta, G.; Mohal, N. preceeding paper.

[4] All new compounds reported here were racemic and characterized on the basis of their spectral data and elemental analyses : **13** δ_H (300 MHz, $CDCl_3$): 4.98 (1H, d, J=5 Hz), 4.59–4.48 (2H, m), 3.91 (1H, dd, J=5, 2 Hz), 3.80–3.67 (2H, m), 3.48 (3H, s), 3.26 (1H, s), 3.13 (3H, s), 2.58 (1H, dd, J=7, 6.5Hz), 1.53 (3H, s), 1.35 (3H, s); δ_C (75 MHz, $CDCl_3$): 113.5 (C), 85.67 (CH), 81.15 (CH), 78.56 (C), 77.73 (CH), 63.06 (CH_2), 58.72 (CH_3), 38.57 (CH_3), 26.06 (CH_3), 24.17 (CH_3). **14** δ_H (300 MHz, $CDCl_3$): 4.94 (1H, d, J=5 Hz), 4.64 (1H, d, J=6 Hz), 4.54 (1H, d, J=6 Hz), 3.97 (1H, d, J=5 Hz), 3.87 (1H, dd, J=12, 5 Hz), 3.69 (1H, d, J=12, 9.5 Hz) 3.56 (3H, s), 3.16 (3H, s), 2.51 (1H, dd , J=9.5, 5 Hz), 1.46 (3H, s), 1.30 (3H, s); δ_C (75 MHz, $CDCl_3$): 111.6(C), 83.79 (CH), 83.62 (CH), 79.35 (CH), 79.32 (C),77.43 (CH), 63.28 (CH_2) ,59.43 (CH_3), 38.06 (CH_3), 25.88 (CH_3), 23.35 (CH_3). **15** δ_H (300 MHz, $CDCl_3$): 4.76 (1H, d, J=7 Hz), 4.56 (1H, dd, J=7.5, 1.5 Hz), 4.03 (1H, dd, J=13, 5 Hz), 3.88 (1H, dd, J=13, 8 Hz), 3.81 (1H, s), 3.64 (1H, d, J=1.5 Hz), 3.45 (3H, s), 1.72 (1H, dd, J=8, 5 Hz, D_2O exchangeable), 1.51 (3H, s), 1.30 (3H, s); δ_C (75 MHz, $CDCl_3$): 113.33 (C), 85.23 (CH), 81.79 (CH), 78.65 (CH), 68.69 (C), 63.53 (CH_2), 59.95 (CH_3), 38.06 (CH_3), 26.08 (CH_3), 25.16 (CH_3). **17** δ_H (300 MHz, D_2O): 4.12-4.10 (1H, m), 3.79(1H, d, J=5 Hz), 3.76-3.68 (2H, m), 3.61-3.52 (2H, m), 3.32 (3H, s); δ_C (75 MHz, D_2O): 82.11 (CH), 78.54 (C), 73.76 (CH), 72.48 (CH), 64.55 (CH_2) ,59.53 (CH), 58.56 (CH_3). **19** δ_H (300 MHz, D_2O): 4.15 (1H, t, J=5.5 Hz), 3.81 (1H, d, J=5 Hz), 3.75-3.68 (3H, series of m), 3.34 (3H, s), 3.24 (1H, d, J=6 Hz); δ_C (75 MHz, D_2O): 88.80 (CH), 79.75 (C), 76.39 (CH), 75.43 (CH), 61.94 (CH_2), 61.09 (CH), 58.58 (CH_3).

[5] Spectral data for synthetic **1**: δ_H (300 MHz, DMSO-d_6): 4.46 (1H, br s), 4.30 (1H, br s), 4.03 (1H, br s), 3.78- 3.73 (1H, m), 3.58-3.56 (1H, m), 3.4 –3.32 (1H, m), 3.29 (3H, s), 1.74 –1.70 (1H, m); δ_C (75 MHz, DMSO-d_6): 88.82, 72.73, 69.37, 66.35, 58.97, 56.72, 51.01. Spectral data reported [2a] for "salpantiol" : δ_H (DMSO-d_6): 4.6 (4H, s), 3.5 (3H, s, OCH_3), 3.2-3.6 (7H, m); δ_C, (DMSO-d_6): 83.48, 72.87, 72.59, 71. 54, 71.44, 70.59, 60.30. Tetraacetate **20**: δ_H (200 MHz, $CDCl_3$): 5.58 –5.52 (1H, m), 5.22- 5.19 (2H, m), 4.22- 4.18 (2H, d, J=8Hz), 3.86 -3.83 (1H, m), 3.39 (3H, s), 2.7- 2.55 (1H, m), 2.10 (3H, s), 2.09 (3H, s), 2.05 (3H, s), 2.02 (3H, s); δ_C (50 MHz, $CDCl_3$): 170.46, 169.95, 169.580, 169.44, 83.45 , 73.72, 70.21, 68.41, 60.96, 58.66, 44.15, 20.61, 20.46.We were unable to obtain an authentic sample or copies of spectra for direct comparison.[2a]