Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: Aurora Aguilera, Carmen Almansa, Albert Moyano & Fèlix Serratora (1991) Stereoselective Synthesis of Tris-endo-tricyclo [5.2.1.$0^{4,10}$]decane-2,5,8-triamine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:15-16, 1643-1648, DOI: 10.1080/00397919108021064

To link to this article: http://dx.doi.org/10.1080/00397919108021064

SYNTHETIC COMMUNICATIONS, 21(15&16), 1643-1648 (1991)

STEREOSELECTIVE SYNTHESIS OF *TRIS-ENDO*-TRICYCLO [5.2.1.$0^{4,10}$]DECANE-2,5,8-TRIAMINE

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ABSTRACT: The title compound has been stereoselectively obtained by a two-step process involving the catalytic hydrogenation of triketone **2** in the presence of benzylamine with a partially deactivated catalyst.

In connection to our work in the field of polyquinane chemistry[1] and particularly in the application of the perhydrotriquinacene skeleton as a concave chiral cap for the construction of enantiodiscriminating hosts,[2] an efficient method for the preparation of *tris-endo*-tricyclo[5.2.1.$0^{4,10}$]decane-2,5,8-triamine **1** was required. Owing to its triple functionalization in the peripheral rim, as well as to its *tris-endo* stereochemistry, this molecule appeared as a particularly suitable starting point for the design and construction of chiral triquinane criptands. We presently describe an efficient method for its preparation from *all-cis*-tricyclo[5.2.1.$0^{4,10}$]decane-2,5,8-trione **2**.[1a,1c,3]

At the outset of our studies on the stereoselective synthesis of **1**, we decided to use a process based on catalytic hydrogenation, since previous work directed to the synthesis of the *tris-endo* triol **3** from

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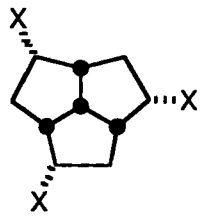
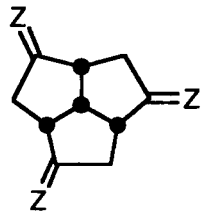
triketone **2** had shown that hydride reduction (either with $LiAlH_4$ or with $NaBH_4$) leads to isomeric mixtures of triols, while catalytic hydrogenation with PtO_2 is totally stereoselective and affords pure **3** in 81% yield.[4]



1 X = NH_2
3 X = OH
7 X = $NHCH_2Ph$



2 Z = O
4 Z = NOH
5 Z = $NOCH_2Ph$
6 Z = NNHTs

In the first place, we tried to synthesize the *tris*-oxime **4**, with the aim of subsequently reducing it by catalytic hydrogenation.[5] Notwithstanding, all of the essays for the formation of **4** using several oxime conditions (NH_2OH .HCl / $BaCO_3$,[6a] NH_2OH.HCl / pyridine,[5d] NH_2OH.HCl / NaOAc[6b] among others) produced mixtures of *mono*-, *bis*- and *tris*-oximes of **2**, not separable by common chromatographic techniques and in which **4** was always present in amounts not superior to 34%, as shown by ^{13}C NMR spectra. We tried also to obtain the *tris*-*O*-benzyloxime **5** by reaction of **2** with benzyloxyamine hydrochloride in methanol in the presence of pyridine,[7] but again inseparable mixtures of *mono*-, *bis*- and *tris*-*O*-benzyloximes were produced, which in the best instance contained a 48 % of **5**. These results agree with those obtained in the synthesis of triquinacene from **2** by means of a triple Shapiro reaction,[8] where mixtures of the *tris*-tosylhydrazone **6** and the corresponding disubstituted derivative were systematically observed.

At this point, we reasoned that the difficulty in effecting in a complete manner the triple substitution of the oxo groups of **2** was probably due to steric hindrance in the addition intermediates, so that

the equilibrium was never totally shifted to the right; if so, this could in principle be overcome by the use of conditions in which the final imine-type product was continously removed from the equilibrium mixture. We decided accordingly to investigate the reductive amination of the triketone **2**.

While direct reductive amination of **2** either with ammonia[9] or benzylamine in a variety of conditions invariably led to complex mixtures (which in the latter case contained appreciable amounts of products arising from polyalquilation of the initially formed amines as shown by GC / MS analysis),[10] we were pleased to find that the hydrogenation (Pd on charcoal, 4 atm, 80 °C) of a mixture of **2** and benzylamine *in the presence of thiophene*[11] led to the formation of the desired *tris*-benzylamino derivative **7** and drastically suppressed the unwanted side reactions of carbonyl reduction and amine polyalkylation. The requisite *tris-endo* stereochemistry of **7** was established by inspection of the ^{13}C NMR spectrum, which exhibited signals of number and intensities corresponding to a molecule of C_3 symmetry. The deprotection of **7** could subsequently be effected in similar reaction conditions (in the absence of thiophene) under prolonged reaction times, affording triamine **1** in 66% yield.

In summary, we have developed an efficient stereoselective synthesis of **1**, which takes place in two steps starting from the tricyclic triketone **2**. It is worth noting that since **2** is readily accessible in optically pure state,[4] the present methodology gives access to triamine **1** in homochiral form.

EXPERIMENTAL

***Tris-endo-N, N', N''*-tribenzyltricyclo[5.2.1.$0^{4,10}$]decane 2,5,8-triamine, 7.**

To a solution of triketone **2** (0.15 g, 0.84 mmol) and benzylamine (0.28 g, 2.55 mmol) in anhydrous methanol (7 mL) are added 0.100 g of

10% Pd / C and 0.8 mL of a thiophene / methanol mixture (1:27). The resulting solution is hydrogenated at 50 °C under atmospheric pressure for 3 days, and then at 80 °C under 4 atm. during 3 additional days. The catalyst is filtered off and the solvent is removed yielding a crude product which is chromatographed on silica gel using a 94:5:1 mixture of CH_2Cl_2 / MeOH /NH_3 as eluent to give 0.122 g (32% yield) of **7** as a colorless oil.

IR ($CHCl_3$): 3600-3140, 3100, 3070, 3040, 2960, 2880, 2820, 1500, 1460, 1350, 1185, 1175, 1030, 740, 700 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz); δ(TMS): 1.31 (q, J = 11.7 Hz, 3H); 1.64 (br s, 3H, NH); 1.78 (m, 3H); 2.49 (m, 3H); 2.69 (p, J = 8.7 Hz, 1H); 3.14 (p, J = 6.3 Hz, 3H); 3.77 (s, 6H); 7.30 (m, 15H).

^{13}C NMR ($CDCl_3$, 50 MHz); δ(TMS): 30.36 (t), 42.90 (d), 49.07 (d), 52.81 (t), 61.37 (d), 126.88 (d), 128.10 (d), 128.36 (d), 140.66 (s).

MS (c. i., NH_3): 452 (M+1).

***Tris-endo*-tricyclo[5.2.1.$0^{4,10}$]decane-2,5,8-triamine, 1.**

To a solution of **7** (0.114 g, 0.25 mmol) in dry ethanol (6 mL) are added 0.50 g of 10% Pd / C. The resulting mixture is hydrogenated at 80 °C under 4 atm. during 3 days. At this point, TLC analysis shows the presence of some starting product. 0.050 g of 10% Pd / C are added and the hydrogenation is continued at the same conditions for 2 additional days. The catalyst is filtered off and the solvent is removed, to give a crude reaction product (0.039 g) which can be purified by washing with $CHCl_3$. In this way pure triamine **1** (0.030 g, 66% yield) is obtained as a colorless oil.

IR (film, NaCl): 3600-3100, 2985, 1590, 1435 cm^{-1}.

^1H NMR (CD_3OD, 200 MHz); δ(TMS): 1.64 (m, 3H); 1.98 (m, 3H); 2.75 (m, 3H); 3.00 (p, J = 9.3 Hz, 1H); 3.53 (m, 3H); 5.01 (br s, 6NH).

^{13}C NMR (CD_3OD, 50 MHz); δ(TMS): 31.91 (t), 45.91 (d), 50.97 (d), 55.85 (d).

MS (c. i., NH_3): 182 (M+1).

The triamine **1** is dissolved in dry methanol and treated dropwise with an ethereal solution of HCl affording the correspoding analytically pure hydrochloride as a white solid which does not melt below 300 °C.

IR (KBr): 3600-2300, 1600, 1495, 1386, 1289, 1195, 1069 cm^{-1}.

Anal. Calculated for $C_{10}H_{19}N_3.3HCl$: C, 41.31%; H, 7.57%; N, 14.46%. Found: C, 41.63%; H, 7.56%; N, 14.88%.

Acknowledgements: We thank Dr. M. Feliz for performing the NMR spectra. Financial support from CAICYT (Proyecto No. 3218/3) and a fellowship from "Ministerio de Educación y Ciencia" to one of us (C. A.) are also gratefully acknowledged.

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(Received in UK 23 April, 1991)