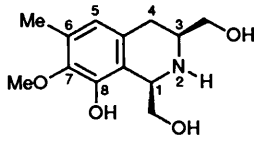
Studies on the Natural β-Adrenergic Receptor Antagonist MY336-a: Synthesis of a 3-Dehydroxymethyl Analogue

Teodoro S. Kaufman
Instituto de Química Orgánica de Síntesis, (CONICET-UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 570, (2000) Rosario, Argentina

The preparation of a polysubstituted tetrahydroisoquinoline, which lacks only the 3-CH_2OH group of MY336-a, is described.

MY336-a **1**, a polysubstituted simple tetrahydroisoquinoline recently isolated from *Streptomyces gabonae* (KY 2234, ATCC



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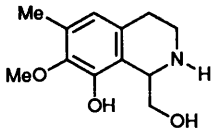


2

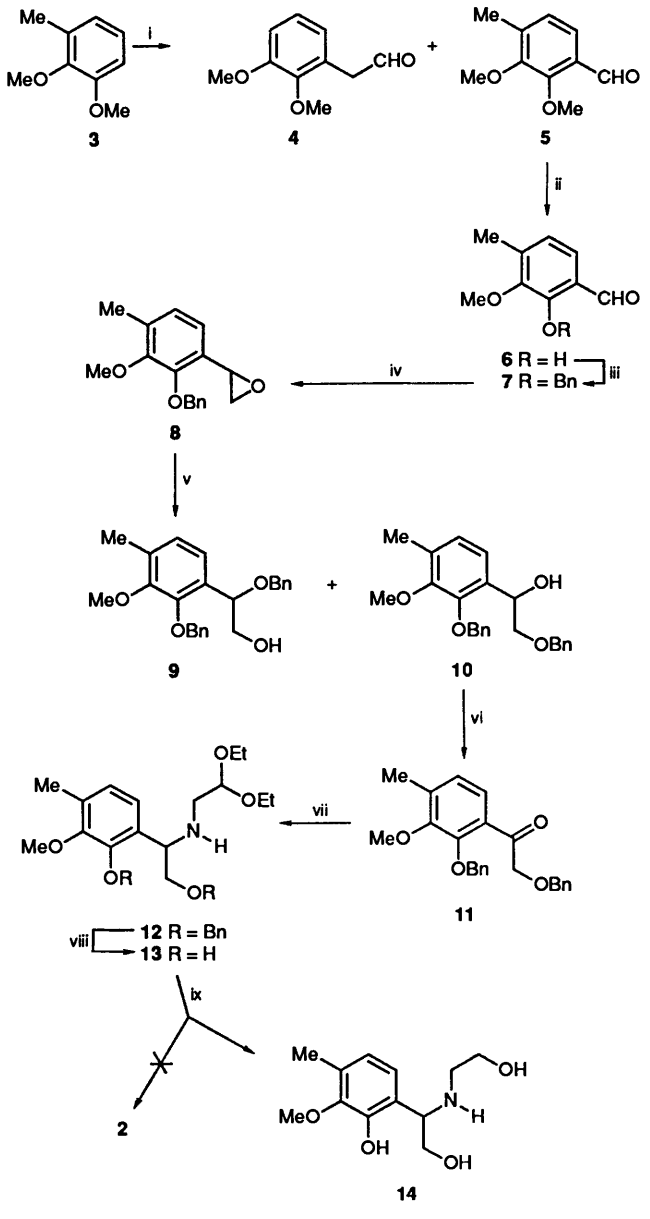
15282),[1] is the first microbial metabolite known to display β-adrenergic receptor antagonism. This communication reports the elaboration of model compound **2**, an analogue of the natural product lacking its 3-CH_2OH group, by acid catalysed cyclisation of a conveniently substituted *N*-benzyl amino acetal derivative obtained from 2,3-dimethoxytoluene **3**.

As outlined in Scheme 1, the synthetic route to **2** started by submission of **3** to a heteroatom-facilitated lithiation with the butyllithium–tetramethylethylenediamine (TMEDA) complex in hexane; dimethylformamide (DMF) quench of the resulting organolithium species and acidic work-up[2] afforded a separable 1:2 mixture of aldehydes **4** and **5*** in 77% combined yield.[3] Anchimerically assisted deprotection of **5** with sodium propyl sulfide in DMF[4] gave phenol **6** which, after benzylation, provided the appropriate substituted intermediate **7** (m.p. 35–36 °C, 72% overall yield).

Incorporation of the C-1 substituent of **2** and synthesis of the key *N*-benzyl amino acetal were carried out in four steps. First, exposure of the aldehyde **7** to dimethylsulfonium methylide under phase transfer conditions furnished the highly acid-sensitive epoxide **8**, which was ring-opened with sodium benzyl oxide in benzyl alcohol, yielding a 1:3 mixture of benzyl ethers **9** and **10** (89% combined yield). Formation of the undesired isomer **9** could not be prevented by varying the reaction conditions, as anticipated by analogy with recent observations regarding the behaviour of styrene oxide under similar conditions.[5]

Then, oxidation of chromatographically purified **10** with pyridinium chlorochromate supported on alumina lead to ketone **11**, whose cyanoborohydride-mediated reductive amination[6] with a five-fold excess of aminoacetaldehyde diethyl acetal finally provided the secondary amine **12** in 76% yield from **10**.

For the last steps, the Bobbitt cyclisation strategy[7] was explored first. Thus, 10% palladium–carbon (Pd–C) catalysed debenzylation of **12** in acidic methanol afforded **13** (93%), which was reacted with hydrochloric acid (5 mol dm^{-3}) followed by a second Pd–C catalytic hydrogenation. Disappointingly, in spite of the variety of reaction conditions investigated, none of them

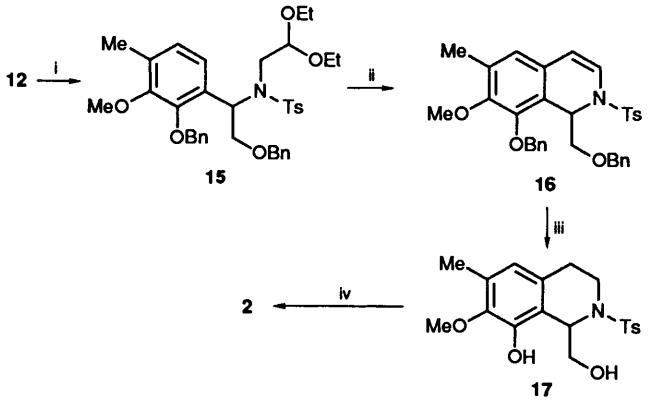


Scheme 1 *Reagents:* i, BuLi, TMEDA, hexane, room temp., 24 h, then DMF (**4** 25%) (**5** 52%); ii, NaH, PrSH, DMF, 90 °C, 1 h (77%); iii, $PhCH_2Cl$, K_2CO_3, EtOH, reflux (94%); iv, $Me_3S^+HSO_4^-$, Bu_4NI (cat.), CH_2Cl_2–50% NaOH aq., reflux, 6 h (100%); v, $NaOPhCH_2$, $PhCH_2OH$, 100 °C, overnight (**9** 23%) (**10** 66%); vi, PCC/Al_2O_3, NaOAc, CH_2Cl_2, reflux (80%); vii, $H_2NCH_2CH(OEt)_2$ (5 equiv.), $NaCNBH_3$, AcOH (4.5 equiv.), $MgSO_4$, EtOH, reflux (95%); viii, H_2 (4 atm), 10% Pd–C, MeOH (93%); ix, HCl (5 mol dm^{-3}), room temp., 18 h, then H_2, 10% Pd–C, 24 h, room temp. (61%)

* All new compounds gave satisfactory spectroscopic data.

furnished the expected product **2**; instead, the main compound isolated consisted of amino alcohol **14** (61%), a fragmented derivative of **1**. The reactivity obtained here for the cyclisation of **13** was quite different from that previously observed in the synthesis of a related tetrahydroisoquinoline, lacking the 6-Me.[8] The substitution of both carbon atoms *ortho* to the methoxy group, which is known to induce an out-of-plane conformation of the latter[9] rendering the aromatic ring less reactive, may account for this unexpected result since the affected substituent, being located *para* to the ring closure position of **13**, facilitates the cyclisation.[7]

As depicted in Scheme 2, in order to overcome this problem



Scheme 2 *Reagents:* i, TsCl, pyridine–$CHCl_3$, reflux (90%); ii, HCl (6 mol dm^{-3}; 8 equiv.), dioxane, reflux, 90 min (90%); iii, H_2 (4 atm), 10% Pd–C, MeOH, 72 h (99%); iv, Na–liq. NH_3, −33 °C, then NH_4Cl (73%)

12 was smoothly converted into sulfonamide **15** (90%) with toluene-*p*-sulfonyl chloride–pyridine and this readily cyclised † to the stable *N*-tosyl-1,2-dihydroisoquinoline **16** (90%) when refluxed in dioxane containing 8 equiv. HCl.[10] Finally, catalytic reduction of **16** over 10% Pd–C (H_2, 4 atm, methanol, 72 h) gave a 99% yield of **17** (m.p. 167–168 °C) and reductive detosylation of **17** with sodium in refluxing liquid ammonia, following the method of du Vigneaud,[11] furnished **2** ‡ (73%) after ammonium chloride quench and column chromatography. This constitutes the first extension of the Jackson modification of the Pomeranz–Fritsch synthesis to the elaboration of a C-1 substituted tetrahydroisoquinoline, avoiding the intermediacy of a fully unsaturated isoquinoline. The application of the above strategy to the total synthesis of MY336-a is currently in progress.

Experimental

8-Benzyloxy-1-benzyloxymethyl-7-methoxy-6-methyl-2-tosyl-1,2-dihydroisoquinoline **16**.—Aqueous HCl (6 mol dm^{-3}; 0.72 cm^3, 4.20 mmol) was added to **15** (340 mg, 0.525 mmol) dissolved in dioxane (6 cm^3) and the mixture was heated at 100 °C under nitrogen. After 30 min, acetal **15** was transformed almost exclusively into the related aldehyde; ν_{max}(film)/cm^{-1} 2924, 2857, 1733, 1455, 1341, 1018 and 699; δ_H(200 MHz; $CDCl_3$) 2.25 (3 H, s), 2.33 (3 H, s), 3.63 (2 H, d, *J* 5.2), 3.74 (3 H, s), 3.81 (2 H, d, *J* 2.0), 4.25 and 4.35 (2 H, ABq, *J* 12.8), 5.02 and 5.12 (2 H, ABq, *J* 12.0), 5.09 (1 H, t, *J* 5.2), 6.80 (2 H, s), 7.04 and 7.53 (4 H, ABq, *J* 8.0), 7.10–7.55 (10 H, m) and 9.28 (1 H, t, *J* 2.0); δ_C(50 MHz; $CDCl_3$) 15.86, 21.34, 53.81, 55.71, 59.92, 70.17, 72.65, 74.92, 123.35, 125.81, 127.49*, 127.59*, 128.14*, 128.24#, 128.43, 128.82#, 129.09*, 133.08, 136.86, 136.98, 137.29, 143.10, 149.51, 151.50 and 200.85. Heating was continued for a further 1 h, then the reaction system was cooled, saturated $NaHCO_3$ (5 cm^3) was added and the reaction products were extracted with EtOAc (3 × 30 cm^3). Drying (Na_2SO_4), concentration and chromatography of the combined organic extracts afforded **16** (263 mg, 0.47 mmol, 90%) as an oil; ν_{max}(film)/cm^{-1} 2972, 2929, 1640, 1506, 1425, 1161 and 957; δ_H(200 MHz; $CDCl_3$) 2.18 (3 H, s), 2.28 (3 H, s), 3.34 (1 H, dd, *J* 5.2, 10.4), 3.53 (1 H, dd, *J* 2.4, 10.4), 3.72 (3 H, s), 4.33 and 4.56 (2 H, ABq, *J* 12.0), 4.71 and 5.04 (2 H, ABq, *J* 11.2), 5.74 (1 H, dd, *J* 2.4, 5.2), 5.91 (1 H, d, *J* 7.2), 6.56 (1 H, s), 6.61 (1 H, d, *J* 7.2), 7.05 and 7.58 (2 H, ABq, *J* 8.0), 7.22 (5 H, s) and 7.40–7.50 (5 H, m); δ_C(50 MHz; $CDCl_3$) 15.61, 21.31, 51.43, 59.99, 69.87, 72.36, 74.63, 112.48, 120.25, 122.16, 123.64, 126.32, 126.67*, 127.15, 127.45*, 127.76*, 128.00#, 128.52*, 129.21*, 131.77, 136.85, 137.37, 138.22, 143.22, 147.55 and 150.58. Two carbon atoms displaying the same chemical shifts are designated with * while three carbons with identical resonances are marked with #; *m/z*(EI) (rel. int.) 555 (M^+, 0.5%), 434 (100), 343 (20), 279 (4), 188 (44), 160 (18) and 91 (65) (Found: M^+, 555.207 24. $C_{33}H_{33}NO_5S$ requires *M*, 555.207 92).

Acknowledgements

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† Prior to cyclisation, acetal **15** completely hydrolysed *in situ* to the related aldehyde, indicating the less reactive nature of its 1,2,3,4-tetrasubstituted aromatic moiety.[10]

‡ ν_{max}(neat)/cm^{-1} 3370, 3130, 2930, 2830, 1620 and 1190; δ_H(200 MHz; D_2O) 2.27 (3 H, s), 2.79–3.06 (2 H, m), 3.19–3.45 (2 H, m), 3.76 (1 H, dd, *J* 9, 11.9), 3.79 (3 H, s), 4.05 (1 H, dd, *J* 4.2, 11.9), 4.55 (1 H, dd, *J* 4.2, 9) and 6.69 (1 H, s); δ_C(50 MHz; D_2O) 16.17, 26.95, 38.05, 54.18, 61.25, 61.47, 119.41, 119.66, 131.20, 132.26, 146.25 and 152.63 (Found: $M^+ - CH_3$, 208.097 17. $C_{11}H_{14}NO_3$ requires $M - CH_3$, 208.097 36).

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