Neurosteroid Analogues. 16. A new explanation for the lack of anesthetic effects of Δ^{16}-alphaxalone and identification of a $\Delta^{17(20)}$ analogue with potent anesthetic activity

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Supporting Information

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Elemental Analysis Results.

5a: Calcd for $C_{20}H_{28}O_3$: C, 75.91 %; H, 8.92 %. Found: C, 75.73%; H, 9.04%.

5b: Calcd for $C_{20}H_{30}O_3$: C, 75.43 %; H, 9.50 %. Found: C, 75.21%; H, 9.73%.

5c: Calcd for $C_{21}H_{31}NO_2$: C, 76.55 %; H, 9.48 %; N, 4.25 %. Found. C, 76.37 %; H, 9.36 %; N, 4.01 %.

6a: Calcd for $C_{21}H_{29}NO_2$: C, 77.02 %; H, 8.93 %; N, 4.28 %. Found. C, 77.17 %; H, 9.13 %; N, 4.26 %.

6b: Calcd for $C_{21}H_{29}NO_2$: C, 77.02 %; H, 8.93 %; N, 4.28 %. Found. C, 76.91 %; H, 8.86 %; N, 4.21 %.

6c: Calcd for $C_{22}H_{31}NO_2$: C, 77.38 %; H, 9.15 %; N, 4.10. Found: C, 77.19 %; H, 9.14 %, N, 3.86 %.

6d: Calcd for $C_{22}H_{31}NO_2$: C, 77.38 %; H, 9.15 %; N, 4.10. Found: C, 77.52 %; H, 9.24 %, N, 4.01 %.

9: Calcd for $C_{22}H_{32}O_4$: C, 73.30 %; H, 8.95 %. Found: C, 73.10 %; H, 8.74 %.

12a: Calcd for $C_{24}H_{33}NO_3$: C, 75.16 %; H, 8.67 %; N, 3.65 %. Found: C, 75.33 %; H, 8.79 %, N, 3.47 %.

12b: Calcd for $C_{24}H_{33}NO_3$: C, 75.16 %; H, 8.67 %; N, 3.65 %. Found: C, 75.33 %; H, 8.66 %, N, 3.60 %.

Table 1. Crystal data and structure refinement for compound **6a** .

Identification code	d33309/lt/ES-88	
Empirical formula	C_{21} H_{29} N O_2	
Formula weight	327.45	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12$	
Unit cell dimensions	a = 9.7973(6) Å	α= 90°.
	b = 23.7370(14) Å	β= 90°.
	c = 7.7783(5) Å	γ = 90°.
Volume	1808.91(19) $Å^3$	
Z	4	
Density (calculated)	1.202 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	712	
Crystal size	0.44 x 0.28 x 0.17 mm^3	
Theta range for data collection	1.72 to 34.03°.	
Index ranges	-15≤h≤15, -37≤k≤36, -12≤l≤11	
Reflections collected	49316	
Independent reflections	7320 [R(int) = 0.0338]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9870 and 0.9674	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7320 / 0 / 220	
Goodness-of-fit on F^2	1.075	
Final R indices [I>2sigma(I)]	R1 = 0.0343, wR2 = 0.0904	
R indices (all data)	R1 = 0.0377, wR2 = 0.0931	
Absolute structure parameter	0.2(6)	
Largest diff. peak and hole	0.355 and -0.175 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for dc33309. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(3)	7720(1)	9448(1)	7324(1)	21(1)
O(11)	5276(1)	7276(1)	10003(1)	31(1)
N(21)	6798(2)	5228(1)	9787(1)	48(1)
C(1)	6341(1)	8450(1)	9112(1)	17(1)
C(2)	6107(1)	9079(1)	9458(1)	19(1)
C(3)	6315(1)	9442(1)	7858(1)	17(1)
C(4)	5484(1)	9220(1)	6351(1)	17(1)
C(5)	5743(1)	8591(1)	6027(1)	13(1)
C(6)	4999(1)	8386(1)	4419(1)	16(1)
C(7)	5368(1)	7775(1)	4001(1)	16(1)
C(8)	5157(1)	7378(1)	5528(1)	12(1)
C(9)	5877(1)	7613(1)	7166(1)	13(1)
C(10)	5439(1)	8222(1)	7633(1)	13(1)
C(11)	5785(1)	7179(1)	8611(1)	17(1)
C(12)	6337(1)	6593(1)	8202(1)	18(1)
C(13)	5562(1)	6365(1)	6629(1)	13(1)
C(14)	5735(1)	6794(1)	5145(1)	12(1)
C(15)	5259(1)	6471(1)	3552(1)	16(1)
C(16)	5885(1)	5883(1)	3849(1)	18(1)
C(17)	6085(1)	5832(1)	5775(1)	15(1)
C(18)	4056(1)	6256(1)	7117(1)	19(1)
C(19)	3923(1)	8244(1)	8158(1)	18(1)
C(20)	6614(1)	5370(1)	6514(1)	23(1)
C(21)	6725(1)	5301(1)	8332(1)	32(1)

Table 3. Bond lengths [Å] and angles [°] for dc33309.

O(3)-C(3)	1.4374(10)
O(3)-H(3)	0.8400
O(11)-C(11)	1.2140(10)
N(21)-C(21)	1.1471(14)
C(1)-C(2)	1.5343(10)
C(1)-C(10)	1.5486(10)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.5270(11)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.5225(11)
C(3)-H(3A)	1.0000
C(4)-C(5)	1.5347(10)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.5271(10)
C(5)-C(10)	1.5537(10)
C(5)-H(5)	1.0000
C(6)-C(7)	1.5303(10)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.5309(10)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(14)	1.5265(9)
C(8)-C(9)	1.5601(10)
C(8)-H(8)	1.0000
C(9)-C(11)	1.5269(10)
C(9)-C(10)	1.5521(9)
C(9)-H(9)	1.0000
C(10)-C(19)	1.5406(10)
C(11)-C(12)	1.5262(10)
C(12)-C(13)	1.5381(10)

C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(17)	1.5177(10)
C(13)-C(18)	1.5454(11)
C(13)-C(14)	1.5478(10)
C(14)-C(15)	1.5297(10)
C(14)-H(14)	1.0000
C(15)-C(16)	1.5419(10)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-C(17)	1.5157(11)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-C(20)	1.3428(10)
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-C(21)	1.4283(14)
C(20)-H(20)	0.9500

C(3)-O(3)-H(3)	109.5
C(2)-C(1)-C(10)	112.62(6)
C(2)-C(1)-H(1A)	109.1
C(10)-C(1)-H(1A)	109.1
C(2)-C(1)-H(1B)	109.1
C(10)-C(1)-H(1B)	109.1
H(1A)-C(1)-H(1B)	107.8
C(3)-C(2)-C(1)	112.73(6)
C(3)-C(2)-H(2A)	109.0
C(1)-C(2)-H(2A)	109.0
C(3)-C(2)-H(2B)	109.0
C(1)-C(2)-H(2B)	109.0
H(2A)-C(2)-H(2B)	107.8

O(3)-C(3)-C(4)	107.02(6)
O(3)-C(3)-C(2)	111.66(6)
C(4)-C(3)-C(2)	111.11(6)
O(3)-C(3)-H(3A)	109.0
C(4)-C(3)-H(3A)	109.0
C(2)-C(3)-H(3A)	109.0
C(3)-C(4)-C(5)	112.04(6)
C(3)-C(4)-H(4A)	109.2
C(5)-C(4)-H(4A)	109.2
C(3)-C(4)-H(4B)	109.2
C(5)-C(4)-H(4B)	109.2
H(4A)-C(4)-H(4B)	107.9
C(6)-C(5)-C(4)	111.40(6)
C(6)-C(5)-C(10)	112.80(6)
C(4)-C(5)-C(10)	112.58(6)
C(6)-C(5)-H(5)	106.5
C(4)-C(5)-H(5)	106.5
C(10)-C(5)-H(5)	106.5
C(5)-C(6)-C(7)	111.30(6)
C(5)-C(6)-H(6A)	109.4
C(7)-C(6)-H(6A)	109.4
C(5)-C(6)-H(6B)	109.4
C(7)-C(6)-H(6B)	109.4
H(6A)-C(6)-H(6B)	108.0
C(6)-C(7)-C(8)	112.80(6)
C(6)-C(7)-H(7A)	109.0
C(8)-C(7)-H(7A)	109.0
C(6)-C(7)-H(7B)	109.0
C(8)-C(7)-H(7B)	109.0
H(7A)-C(7)-H(7B)	107.8
C(14)-C(8)-C(7)	110.96(6)
C(14)-C(8)-C(9)	108.46(5)
C(7)-C(8)-C(9)	110.60(5)
C(14)-C(8)-H(8)	108.9
C(7)-C(8)-H(8)	108.9
C(9)-C(8)-H(8)	108.9

C(11)-C(9)-C(10)	116.13(6)
C(11)-C(9)-C(8)	109.41(6)
C(10)-C(9)-C(8)	113.55(5)
C(11)-C(9)-H(9)	105.6
C(10)-C(9)-H(9)	105.6
C(8)-C(9)-H(9)	105.6
C(19)-C(10)-C(1)	109.99(6)
C(19)-C(10)-C(9)	111.05(5)
C(1)-C(10)-C(9)	109.95(5)
C(19)-C(10)-C(5)	112.31(6)
C(1)-C(10)-C(5)	106.91(6)
C(9)-C(10)-C(5)	106.49(5)
O(11)-C(11)-C(12)	120.26(7)
O(11)-C(11)-C(9)	123.58(7)
C(12)-C(11)-C(9)	116.13(6)
C(11)-C(12)-C(13)	108.12(6)
C(11)-C(12)-H(12A)	110.1
C(13)-C(12)-H(12A)	110.1
C(11)-C(12)-H(12B)	110.1
C(13)-C(12)-H(12B)	110.1
H(12A)-C(12)-H(12B)	108.4
C(17)-C(13)-C(12)	118.29(6)
C(17)-C(13)-C(18)	106.90(6)
C(12)-C(13)-C(18)	109.57(6)
C(17)-C(13)-C(14)	100.60(5)
C(12)-C(13)-C(14)	107.93(5)
C(18)-C(13)-C(14)	113.46(6)
C(8)-C(14)-C(15)	119.98(6)
C(8)-C(14)-C(13)	114.22(6)
C(15)-C(14)-C(13)	103.95(5)
C(8)-C(14)-H(14)	105.9
C(15)-C(14)-H(14)	105.9
C(13)-C(14)-H(14)	105.9
C(14)-C(15)-C(16)	102.18(6)
C(14)-C(15)-H(15A)	111.3
C(16)-C(15)-H(15A)	111.3

C(14)-C(15)-H(15B)	111.3
C(16)-C(15)-H(15B)	111.3
H(15A)-C(15)-H(15B)	109.2
C(17)-C(16)-C(15)	105.71(6)
C(17)-C(16)-H(16A)	110.6
C(15)-C(16)-H(16A)	110.6
C(17)-C(16)-H(16B)	110.6
C(15)-C(16)-H(16B)	110.6
H(16A)-C(16)-H(16B)	108.7
C(20)-C(17)-C(16)	122.50(7)
C(20)-C(17)-C(13)	128.63(7)
C(16)-C(17)-C(13)	108.85(6)
C(13)-C(18)-H(18A)	109.5
C(13)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(13)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(10)-C(19)-H(19A)	109.5
C(10)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(10)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(17)-C(20)-C(21)	123.20(8)
C(17)-C(20)-H(20)	118.4
C(21)-C(20)-H(20)	118.4
N(21)-C(21)-C(20)	177.83(13)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for dc33309. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(3)	18(1)	20(1)	26(1)	-7(1)	0(1)	-2(1)
O(11)	62(1)	19(1)	12(1)	1(1)	7(1)	6(1)
N(21)	87(1)	30(1)	28(1)	6(1)	-7(1)	28(1)
C(1)	22(1)	15(1)	14(1)	-2(1)	-4(1)	1(1)
C(2)	23(1)	16(1)	17(1)	-5(1)	-2(1)	2(1)
C(3)	17(1)	13(1)	19(1)	-3(1)	-1(1)	1(1)
C(4)	20(1)	13(1)	18(1)	0(1)	-3(1)	1(1)
C(5)	15(1)	12(1)	13(1)	0(1)	-1(1)	0(1)
C(6)	21(1)	14(1)	13(1)	2(1)	-3(1)	-1(1)
C(7)	24(1)	13(1)	10(1)	1(1)	-1(1)	-1(1)
C(8)	16(1)	12(1)	10(1)	0(1)	-1(1)	0(1)
C(9)	16(1)	12(1)	10(1)	0(1)	-1(1)	1(1)
C(10)	15(1)	12(1)	11(1)	-1(1)	0(1)	0(1)
C(11)	28(1)	14(1)	10(1)	1(1)	-3(1)	1(1)
C(12)	26(1)	15(1)	13(1)	1(1)	-4(1)	4(1)
C(13)	16(1)	12(1)	11(1)	1(1)	-1(1)	2(1)
C(14)	15(1)	12(1)	10(1)	0(1)	0(1)	-1(1)
C(15)	22(1)	13(1)	12(1)	-1(1)	-2(1)	-1(1)
C(16)	25(1)	14(1)	15(1)	-2(1)	-1(1)	0(1)
C(17)	18(1)	13(1)	15(1)	0(1)	0(1)	0(1)
C(18)	20(1)	17(1)	21(1)	5(1)	6(1)	1(1)
C(19)	17(1)	18(1)	18(1)	-1(1)	4(1)	0(1)
C(20)	31(1)	17(1)	20(1)	0(1)	-2(1)	8(1)
C(21)	51(1)	19(1)	27(1)	3(1)	-4(1)	16(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for dc33309.

	x	y	z	U(eq)
H(3)	8183	9636	8031	32
H(1A)	6142	8235	10173	20
H(1B)	7313	8389	8818	20
H(2A)	5165	9134	9888	22
H(2B)	6744	9206	10367	22
H(3A)	6021	9837	8118	20
H(4A)	5722	9435	5303	20
H(4B)	4501	9279	6586	20
H(5)	6741	8551	5788	16
H(6A)	5246	8630	3434	19
H(6B)	4002	8416	4600	19
H(7A)	6335	7758	3636	19
H(7B)	4800	7645	3026	19
H(8)	4157	7343	5762	15
H(9)	6868	7638	6866	15
H(12A)	6202	6340	9198	21
H(12B)	7326	6614	7949	21
H(14)	6741	6847	5002	15
H(15A)	5612	6645	2485	19
H(15B)	4250	6452	3495	19
H(16A)	5263	5585	3426	22
H(16B)	6770	5849	3242	22
H(18A)	3559	6118	6108	29
H(18B)	3639	6608	7519	29
H(18C)	4014	5974	8034	29
H(19A)	3795	8035	9233	27
H(19B)	3365	8073	7251	27
H(19C)	3646	8637	8323	27
H(20)	6928	5075	5791	27

Table 6. Torsion angles [°] for dc33309.

C(10)-C(1)-C(2)-C(3)	-55.66(9)
C(1)-C(2)-C(3)-O(3)	-67.57(8)
C(1)-C(2)-C(3)-C(4)	51.83(9)
O(3)-C(3)-C(4)-C(5)	69.80(8)
C(2)-C(3)-C(4)-C(5)	-52.34(8)
C(3)-C(4)-C(5)-C(6)	-175.07(6)
C(3)-C(4)-C(5)-C(10)	57.07(8)
C(4)-C(5)-C(6)-C(7)	174.52(6)
C(10)-C(5)-C(6)-C(7)	-57.73(8)
C(5)-C(6)-C(7)-C(8)	53.10(8)
C(6)-C(7)-C(8)-C(14)	-171.44(6)
C(6)-C(7)-C(8)-C(9)	-51.02(8)
C(14)-C(8)-C(9)-C(11)	-51.90(7)
C(7)-C(8)-C(9)-C(11)	-173.80(6)
C(14)-C(8)-C(9)-C(10)	176.57(6)
C(7)-C(8)-C(9)-C(10)	54.67(8)
C(2)-C(1)-C(10)-C(19)	-65.91(8)
C(2)-C(1)-C(10)-C(9)	171.50(6)
C(2)-C(1)-C(10)-C(5)	56.29(8)
C(11)-C(9)-C(10)-C(19)	-62.39(8)
C(8)-C(9)-C(10)-C(19)	65.76(7)
C(11)-C(9)-C(10)-C(1)	59.58(8)
C(8)-C(9)-C(10)-C(1)	-172.28(6)
C(11)-C(9)-C(10)-C(5)	175.06(6)
C(8)-C(9)-C(10)-C(5)	-56.80(7)
C(6)-C(5)-C(10)-C(19)	-63.57(8)
C(4)-C(5)-C(10)-C(19)	63.55(7)
C(6)-C(5)-C(10)-C(1)	175.69(6)
C(4)-C(5)-C(10)-C(1)	-57.18(8)
C(6)-C(5)-C(10)-C(9)	58.19(7)
C(4)-C(5)-C(10)-C(9)	-174.69(6)
C(10)-C(9)-C(11)-O(11)	7.28(12)
C(8)-C(9)-C(11)-O(11)	-122.86(9)
C(10)-C(9)-C(11)-C(12)	-174.61(6)

C(8)-C(9)-C(11)-C(12)	55.25(9)
O(11)-C(11)-C(12)-C(13)	120.46(9)
C(9)-C(11)-C(12)-C(13)	-57.72(9)
C(11)-C(12)-C(13)-C(17)	169.60(6)
C(11)-C(12)-C(13)-C(18)	-67.59(7)
C(11)-C(12)-C(13)-C(14)	56.40(8)
C(7)-C(8)-C(14)-C(15)	-55.59(8)
C(9)-C(8)-C(14)-C(15)	-177.27(6)
C(7)-C(8)-C(14)-C(13)	-179.97(6)
C(9)-C(8)-C(14)-C(13)	58.35(7)
C(17)-C(13)-C(14)-C(8)	174.18(6)
C(12)-C(13)-C(14)-C(8)	-61.25(7)
C(18)-C(13)-C(14)-C(8)	60.37(8)
C(17)-C(13)-C(14)-C(15)	41.62(7)
C(12)-C(13)-C(14)-C(15)	166.19(6)
C(18)-C(13)-C(14)-C(15)	-72.18(7)
C(8)-C(14)-C(15)-C(16)	-170.38(6)
C(13)-C(14)-C(15)-C(16)	-41.24(7)
C(14)-C(15)-C(16)-C(17)	24.33(7)
C(15)-C(16)-C(17)-C(20)	179.83(8)
C(15)-C(16)-C(17)-C(13)	1.51(8)
C(12)-C(13)-C(17)-C(20)	38.40(11)
C(18)-C(13)-C(17)-C(20)	-85.74(10)
C(14)-C(13)-C(17)-C(20)	155.56(8)
C(12)-C(13)-C(17)-C(16)	-143.41(7)
C(18)-C(13)-C(17)-C(16)	92.45(7)
C(14)-C(13)-C(17)-C(16)	-26.25(7)
C(16)-C(17)-C(20)-C(21)	-175.71(9)
C(13)-C(17)-C(20)-C(21)	2.26(15)
C(17)-C(20)-C(21)-N(21)	133(3)

Projection view with 50% thermal ellipsoids: