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A stereocontrolled access to 9-methyl cyclobuta[*a*]indan: en route to rigid atipamezole analogues

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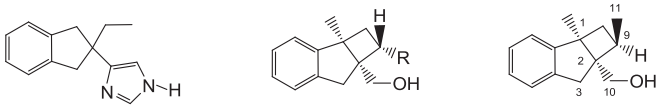
ABSTRACT

This work deals with the preparation of a benzofused bicyclo[3.2.0]heptane intermediate en route to rigid analogues of atipamezole. We show that an intramolecular hydrosilylation in which a hydroxyl group serves as directing element can be used for the stereoselective synthesis of the target compound **7** from the *exo*-methylene derivative **4**. The Si–H addition onto the proximal double bond is regioselective and the cyclization occurs exclusively via a 5-*exo*-*trig* mode. Although the γ-silyl alcohol **8a** resisted 1,4-Brook-type rearrangement, its sodium salt was found to cyclize under thermal conditions to give the siloxacyclopentane **6a** in good yield.

1. Introduction

Over the past years our team has been involved in the study of conformationally rigid analogues of atipamezole,[1] a selective α_2 adrenergic antagonist used in veterinary medicine (Fig. 1). Our goal was to discover improved α_2 receptor ligands as potential new therapeutics for neurodegenerative diseases,[2] a domain wherein the medical need is in high demand.[3] To this end, we locked the conformation of the indan core of atipamezole by fusion with a cyclopropane[4a] or a cyclobutane[4b] ring and restricted rotation about the C2–C10 axis by incorporating a substituent at the C9 position. This strategy resulted in molecules that proved far superior to atipamezole at boosting noradrenaline turnover in the mouse cortex after systemic dosing,[2] a feature that makes it possible to explore noradrenaline (NA) modulation beyond the limits set with established NA re-uptake inhibitors and other α_2 antagonists.



Atipamezole Ref 5 This work

Fig. 1. Towards rigid analogues of atipamezole.

We recently disclosed a stereocontrolled route to (1*R**,2*S**,9*S**)-cyclobutane derivatives from cyclobutanone **1** (Scheme 1).[5] The approach developed combined a silicon assisted intramolecular ring closure metathesis with a diastereoselective hydrogenation of the newly created double bond in favour of the *cis*-junction between the four- and seven-membered rings (Fig. 2, equation a). We have now investigated the intramolecular hydrosilylation as a complementary means by which to reach the opposite (1*R**,2*S**,9*R**)-cyclobutane stereoisomer from **1**. In this undertaking, the regioselectivity of the Si–H addition into the exocyclic double bond was of little concern as both regioisomers would converge to the same desilylated product (Fig. 2, equation b). From literature data, it was assumed that the hydrosilylation is *syn*, i.e., the Si and H atoms both enter from the same face as the alcohol function,[6] and that the protonolysis of the C–Si bond occurs with retention of configuration at carbon.[7]

Catalytic hydrosilylation of alkenes is one of the main routes to organosilicon derivatives.[8] The intramolecular variant of this reaction, in particular when coupled with oxidative cleavage of the resultant carbon–silicon bond represents an efficient method[9] for the regio- and stereoselective synthesis of 1,3-diols[10] and polyhydroxylated molecules from alkenols.[11] In their pioneering work, Tamao and Ito have delineated ring size and substituent effects on the regioselectivity of the intramolecular hydrosilylation of allylic and homoallylic hydridosilyl ethers catalysed by Pt and Rh.[10a,b] Enantioselectivity was next achieved by Bosnich.[12]

Herein, we show that the intramolecular hydrosilylation of the *exo*-methylene derivative **5** occurred with complete but opposite regioselectivity to that predicted from literature data. We also present the facile interconversion between the ring-closed (**6a**, Scheme 1) and ring opened (**8a**, Scheme 2) silicon containing

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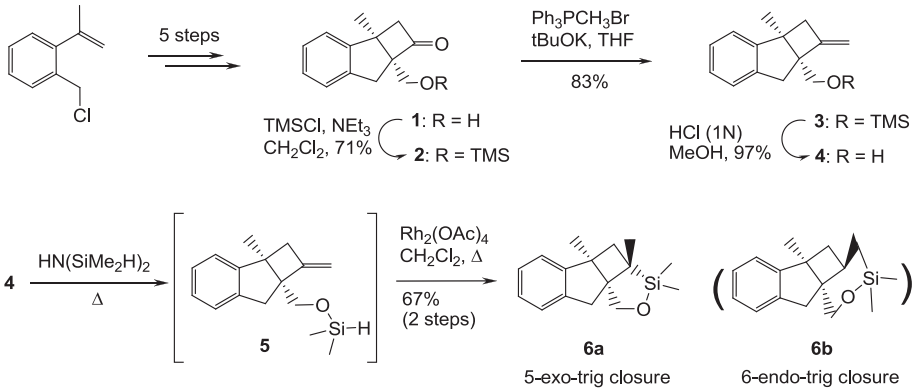


Scheme 1. Preparation of siloxane **6**.

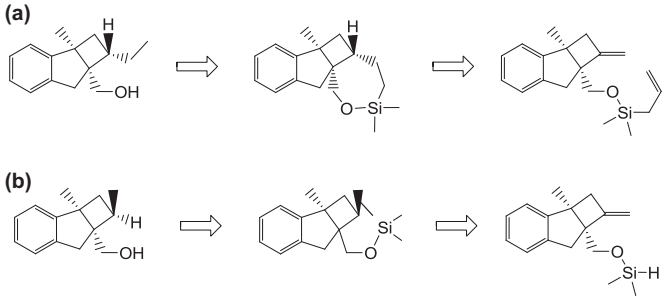
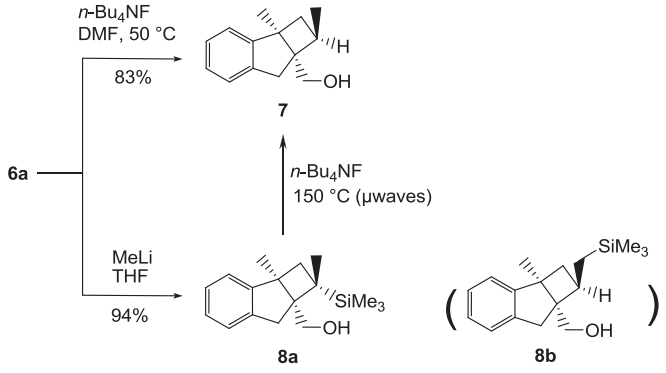


Fig. 2. Control of the relative stereochemistry at C9.

derivatives in which a methyl carbanion acts either as a nucleofuge or as a nucleophile, respectively.



Scheme 2. Preparation of (1*R**,2*S**,9*R**)-methyl derivative **7**.

2. Results and discussion

Retrosynthetically, the hydrosilylation precursor **5** was derived from the homoallylic alcohol **4**, which, in turn, was traced back to the keto alcohol **1** (Scheme 1). We have previously reported the synthesis of racemic **1** in five steps from 2-isopropenyl-benzyl chloride.[5] Protection of **1** as a trimethylsilyl ether (**2**) followed by methylenation of the ketone under Wittig conditions afforded the exocyclic methylene derivative **3**. Cleavage of the TMS group by treatment with methanolic HCl gave the target alcohol **4** (Scheme 1).

Several silylating agents (i.e., $ClSiMe_2H$,[13] $CF_3SO_3SiMe_2$,[14] $HN(SiMe_2H)_2$[15]) and conditions were tested to access the hydridosilyl ether **5** from alcohol **4**. Eventually, heating **4** in neat 1,1,3,3-tetramethyldisilazane (10 equiv) delivered the unstable intermediate **5** reproducibly, and in sufficient purity to avoid further manipulations other than stripping excess of $HN(SiMe_2H)_2$.

With a method to prepare **5** secured, we next examined the key Si–C bond-forming step. Surprisingly, chloroplatinic acid,[16] the most widespread hydrosilylation catalyst, proved not suitable for this transformation. Adapting Leighton's conditions[17] ($Rh(acac)(CO)_2$, using toluene instead of benzene) turned out to be more productive and gave an encouraging 40% of the cyclized product **6a**. Further, compound **6a** was stable enough to withstand isolation by flash chromatography on neutral alumina. These results prompted us to survey alternative neutral rhodium catalysts for the hydrosilylation of crude **5**.[18] Both Rh(I) and Rh(II) complexes[19] reacted much alike, whereas, in our hands, Rh(III) exhibited no catalytic activity.[20] In the case of $Rh_2(OAc)_4$, the nature of the aprotic solvent (heptane, toluene, dichloromethane, dichloroethane, dioxane) had no major influence on the outcome and high dilution was not necessary. Finally, we settled on $Rh_2(OAc)_4$ in refluxing CH_2Cl_2 for gram-scale preparation of **6a**. Attempts to perform a one-pot O-silylation–hydrosilylation sequence were of no avail.[21]

The presence of a substituent on the internal olefinic carbon of but-3-en-1-ol systems is known to preclude *exo*-cyclization of the corresponding hydridosilyl ethers.[22,23] Nonetheless, hydrosilylation of **5** did not yield **6b** but led to the 5-*exo-trig* product **6a** instead, the silyl group being introduced on the sterically more hindered olefinic terminus. This reversal of selectivity, as well as the unexpected lack of catalytic activity of H_2PtCl_6,[24a] raised the possibility of a departure from the classical Chalk and Harrod's mechanism.[8,24b] In fact, the geometrical requirements for olefin insertion into the Rh–Si (**5A**→**5B**) or Rh–H (**5A**→**5B′** or **5C**) bonds seem in all cases accessible,[25] however the polarization of the C–Rh bond might add stabilization to the intermediates **5B** and **5C** over the rhodacycle **5B′** (Fig. 3).

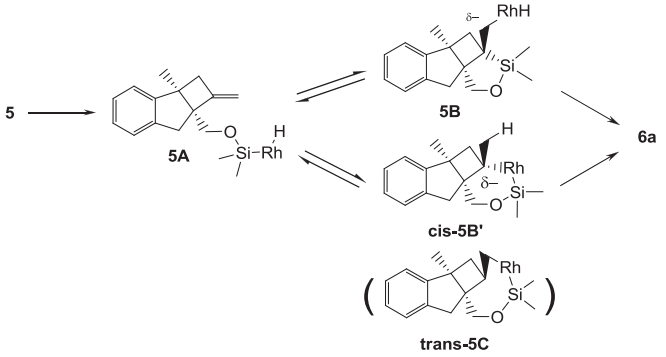


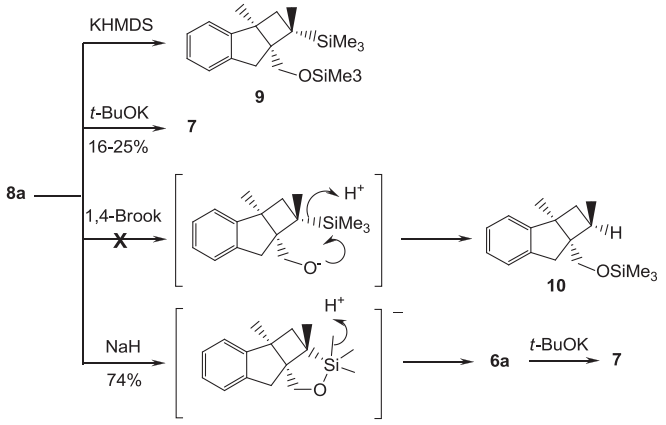
Fig. 3. Mechanisms accounting for the formation of **6a**.

Despite the built-in strain of the tetracyclic system, which contains three contiguous tetrasubstituted carbons, the yield of **6a** was acceptable. We unambiguously confirmed the regioselectivity

of the hydrosilylation step by chemical correlation. Accordingly, the siloxacyclopentane **6a** was converted almost quantitatively into the ring open derivative **8a** by treatment with salt-free MeLi (Scheme 2);[27] **8b** remained undetected in the reaction. In any case, we consider that the isolation of **8a** definitely sealed the issue of the cyclization regiochemistry.

Removal of the Si tether from **6a** proceeded smoothly with *n*-Bu_4NF in hot DMF releasing the alcohol **7** with retention of configuration at carbon.[26] Not unexpectedly, the protonolysis of the Me_3Si group from **8a** turned out to be extremely difficult (Scheme 2). Overall, the isolation of **7** demonstrates that the approach outlined in Fig. 2 (path b) is feasible.

The temperature gap between the F^- mediated desilylation of **8a** and **6a** (150 vs 50 °C, respectively) highlights the difference in the electrophilicity of their Si atoms. On this basis, it was anticipated that the oxidative cleavage of the C9–Si bond in **6a** would be facilitated.[7,9–11,28,29] Before exploring this avenue, we were drawn to examine the 1,4-Brook rearrangement from **8a** (Scheme 3),[30,31] as it would open a direct, stereoselective access to quaternary carbon at C9. Notwithstanding the well suited spatial relationship between the OH and Si groups, chances were remote given the lack of stabilization of the developing negative charge at C9 position. Under Smith's conditions (KHMDS, THF),[32] the silyl ether **10** was not generated in any detectable amount, even after prolonged reaction times. Heating the mixture (150 °C, 5 min) returned the bissilylated derivative **9** as the only identifiable product.[33] In contrast, when *t*-BuOK (5 equiv) was used as base in order to quench the putative Brook carbanion as it formed with conjugated *t*-BuOH,[34] **7** was obtained in 16% yield; hexamethylphosphoramide as additive (5% v/v) increased the yield to 25%.[35] All attempts at trapping the carbanion at C9 with an external electrophile, such as MeI or $PhCH_2Br$ failed, which indeed undermined the contribution of a Brook-type rearrangement. To further probe this point we performed a series of irreversible deprotonation experiments.



Scheme 3. Reactions of **8a** under basic conditions.

Subjecting **8a** to an excess of KH (3 equiv) produced a complex mixture was from which only **6a** could be characterized as a minor component.[36] On the other hand, pyrolysis of the sodium alkoxide of **8a** (NaH, 130 °C) also gave back the siloxacycle **6a** but this time as a single product in 74% yield. A methyl instead of the TMS group is therefore displaced from the Si atom by the alkoxide function at C10, most likely through a pentacoordinated silicate anion intermediate. Consistent with this hypothesis, C–Si bonds in hypervalent silicon species are known to be activated towards electrophiles and methyl is the more labile amongst the saturated alkyl groups.[37] Further, Si rehybridization from a tetrahedral to a trigonal-bipyramide complex may be energetically favoured by alleviating bond-angle strain.[38] Compound **6a**, like its congener **8a**, underwent desilylation upon treatment with *t*-BuOK (Scheme 3),[39] presumably via nucleophilic attack of *t*-BuO^- on the Si atom of **6a**.[40] The contribution of a Brook-type mechanism in the desilylation of **8a** can thus be ruled out.

3. Conclusion

A major issue confronted in the chemistry of this novel series of rigid α_2 receptor ligands concerned the introduction of a substituent at C9 in a stereocontrolled fashion. We have now completed the preparation of 1-methyl-2-(hydroxymethyl)-9-methylcyclobuta[*a*]indane **7** and show that the latter can be synthesized in diastereoisomerically pure (1*R**,2*S**,9*R**)-form through an intramolecular hydrosilylation–desilylation sequence starting from the exocyclic methylene derivative **5**.

Contrary to expectation, hydrosilylation of **5** occurred with complete 5-*exo* regioselectivity to give the stable siloxacyclopentane **6a**. The cyclization mode suggests that the mechanism of the hydrosilylation might deviate from that of Chalk–Harrod's. Further, the addition of Si onto the more hindered carbon of the double bond indicates that substitution at the terminal sp^2 carbon in the olefinic precursor might be tolerated. This would expand the scope of the present strategy to the synthesis of analogues of **7** for SAR studies.

Although **8a** resisted 1,4-Brook rearrangement, we found that the sodium alkoxide of **8a** cyclised under thermal conditions to give the siloxacyclopentane **6a** effectively, a pathway strikingly sensitive to the alkoxide countercation (Na^+ vs K^+). The synthetic potential of **6a** is currently being investigated further.

4. Experimental section

4.1. General experimental methods

Melting points were not corrected. ^1H NMR chemical shifts are reported in δ value (ppm) relative to an internal standard of tetramethylsilane. HRMS were performed on a time-of-flight mass analyser. Analytical thin-layer chromatography was carried out on pre-coated plates. Experiments under microwave irradiation were conducted in a Biotage Initiator reactor (external surface sensor for temperature monitoring). The connectivity between the trimethylsilyl group and the carbon at C9 in compound **8a** was ascertained by NMR HMBC and NOESY ^1H–^1H. The relative stereochemistry at C9 in compound **7** was assigned by NMR NOESY ^1H–^1H (cf. Supplementary data).

4.1.1. (1R,2S*)-1-Methyl-2-(trimethylsilanyloxymethyl)-cyclobuta[1,2-a]indan-9-one (**2**).* To a solution of **1**[5] (4.09 g, 20.22 mmol, 1 equiv) in CH_2Cl_2 (120 mL), triethylamine (3.53 mL, 25.27 mmol, 1.25 equiv) and dimethylaminopyridine (0.12 g, 1 mmol, 0.05 equiv) maintained at −20 °C under an argon atmosphere was added dropwise trimethylchlorosilane (2.26 mL, 24.26 mmol, 1.2 equiv). The mixture was stirred for 1 h 30 min at 0 °C then poured into ice water, decanted and the aqueous phase extracted twice with dichloromethane. The organic layers were combined, washed with H_2O, brine then dried (Na_2SO_4), filtered and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane then heptane/ethyl acetate, 95:5) to afford 3.55 g (71%) of **2**: ^1H NMR (400 MHz, $CDCl_3$, δ): 0.15 (s, 9H), 1.74 (s, 3H), 2.73 (d, *J*=16.8 Hz, 1H), 2.94 (d, *J*=17.2 Hz, 1H), 3.18 (d, *J*=16.8 Hz, 1H), 3.25 (d, *J*=17.2 Hz, 1H), 3.81 (d, *J*=10.8 Hz, 1H), 3.99 (d, *J*=10.8 Hz, 1H), 7.14–7.21 (m, 2H), 7.23–7.26 (m, 2H).

4.1.2. (1R,2S*)-1-Methyl-2-(trimethylsilanyloxymethyl)-cyclobuta[1,2-a]indan-9-methylene (**3**).* To a suspension of methyltriphenylphosphonium bromide (7.58 g, 21.22 mmol, 1.6 equiv) in

THF (180 mL) at room temperature under an argon atmosphere was added portionwise potassium *tert*-butoxide (2.68 g, 23.88 mmol, 1.8 equiv). The mixture was stirred for 3 h at room temperature then a solution of **2** (3.28 g, 13.26 mmol, 1 equiv) in THF (20 mL) was added dropwise and the mixture stirred for an additional 4 h. The mixture was concentrated under reduced pressure then ice water added and the aqueous solution extracted with ethyl acetate. The organic layers were combined, washed with brine then dried (Na_2SO_4), filtered and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 95:5) to afford 3 g (83%) of **3**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.11 (s, 9H), 1.43 (s, 3H), 2.59 (d, J=15.2 Hz, 1H), 2.83 (dt, J=15.2, 2.8 Hz, 1H), 2.93 (d, J=16.0 Hz, 1H), 3.18 (d, J=16.0 Hz, 1H), 3.73 (d, J=10.4 Hz, 1H), 3.86 (d, J=10.4 Hz, 1H), 4.79 (s, 1H), 4.97 (t, J=2.8 Hz, 1H), 7.16–7.19 (m, 4H).

4.1.3. (1R,2S*)-1-Methyl-2-(hydroxymethyl)-cyclobuta[1,2-a]indan-9-methylene (**4**).* To a solution of **3** (2.22 g, 8.14 mmol, 1 equiv) in methanol (50 mL) at room temperature was added an aqueous solution of HCl (1 N, 12.20 mL, 12.2 mmol, 1.5 equiv) and the mixture stirred at room temperature for 1 h 30 min. The methanol was removed under reduced pressure then the residue diluted with water and extracted with diethyl ether. The organic layers were combined, washed with brine then dried (Na_2SO_4), filtered and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 9:1) to afford 1.58 g (97%) of **4**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.47 (s, 3H), 1.56 (t, J=4.8 Hz, 1H), 2.65 (dt, J=15.6, 2.0 Hz, 1H), 3.06 (s, 2H), 3.83–3.91 (m, 2H), 4.90 (t, J=2.0 Hz, 1H), 4.79 (s, 1H), 5.06 (t, J=2.8 Hz, 1H), 7.17–7.24 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.5 (C12), 40.9 (C3), 45.3 (C8), 50.2 (C1), 60.3 (C2), 64.6 (C10), 108.1 (C11), 123.4 (CH), 125.0 (CH), 126.8 (CH), 127.0 (CH), 141.9 (C3a), 150.7 (C9), 152.1 (C7a); IR (neat) ν: 3396, 3066, 3017, 2946, 2919, 2865, 1671, 1480, 1458, 1048, 1013, 759 cm^{-1}; HRMS-ESI (m/z): 223.1102 $[M+23]^+$ calcd for $C_{14}H_{16}NaO$: 223.1093; purity HPLC: 97.6% (Xbridge C18 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 7:3, t_R 4.7 min).

4.1.4. (1R,2S*,9S*)-1,9-Dimethyl-oxasilacyclopenta[2,9]-cyclobuta[1,2-a]indan (**6a**).* Compound **4** (1.32 g, 6.59 mmol, 1 equiv) in neat 1,1,3,3-tetramethyldisilazane (9.1 mL, 52.7 mmol, 8 equiv) was heated at 110 °C for 3 h under an argon atmosphere. The cooled mixture was concentrated under reduced pressure then taken up in toluene and concentrated again. The mixture was taken up in dichloromethane (30 mL) then dirhodium tetracetate (0.145 g, 0.33 mmol, 0.05 equiv) was added in one portion and the mixture maintained under an argon atmosphere heated at reflux for 2 h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (neutral alumina, dichloromethane) to afford 1.1 g (67%) of **6a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.11 (s, 3H), 0.30 (s, 3H), 1.00 (s, 3H), 1.36 (s, 3H), 1.67 (d, J=12 Hz, 1H), 2.27 (d, J=12 Hz, 1H), 2.66 (d, J=17.4 Hz, 1H), 3.12 (d, J=17.4 Hz, 1H), 3.65 (d, J=11.0 Hz, 1H), 4.15 (d, J=11.0 Hz, 1H), 7.09–7.19 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −4.2 (CH_3Si), −3.2 (CH_3Si), 17.4 (C11), 20.5 (C12), 25.2 (C9), 36.1 (C3), 43.4 (C8), 53.0 (C1), 55.7 (C2), 69.7 (C10), 122.4 (CH), 124.3 (CH), 126.5 (CH), 127.0 (CH), 141.7 (C3a), 153.4 (C7a); IR (neat) ν: 2950, 2921, 2855, 1251, 1048, 1015, 856, 823, 759 cm^{-1}; HRMS-ESI (m/z): 281.1338 $[M+23]^+$ calcd for $C_{16}H_{22}NaOSi$: 281.1347; (m/z): 299.1434 $[M+23+18]^+$ calcd for $C_{16}H_{24}NaO_2Si$: 299.1437; purity HPLC: 96.9% (Xbridge C18 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 7:3, t_R 13.1 min).

4.1.5. (1R,2S*,9R*)-1,9-Dimethyl-2-(hydroxymethyl)-cyclobuta[1,2-a]indan (**7**).* To a solution of **6a** (0.40 g, 1.54 mmol, 1 equiv) in DMF (16 mL) at room temperature under an argon atmosphere was added a solution of tetrabutylammonium fluoride in THF (1 M, 16 mL, 16 mmol, 10 equiv). The mixture was stirred at 50 °C overnight then concentrated under reduced pressure. The residue was taken up in brine and extracted with diethyl ether. The organic layers were combined, washed with brine then dried (Na_2SO_4), filtered and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 9:1) to afford 0.26 g (83%) of **7**, which crystallized at 4 °C (low melting solid); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.91 (d, J=4 Hz, 3H), 1.30 (s, 1H), 1.38 (s, 3H), 1.56 (dq, J=12, 4 Hz, 1H), 2.24–2.34 (m, 2H), 9.99 (d, J=16 Hz, 1H), 3.14 (d, J=16 Hz, 1H), 3.80 (m, 2H), 7.90 (d, 1H), 710–7.22 (m, 2H), 7.23 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 16.9 (C11), 20.8 (C12), 30.0 (C9), 35.8 (C8), 41.3 (C3), 49.6 (C1), 52.6 (C2), 67.8 (C10), 122.4 (CH), 124.5 (CH), 126.5 (CH), 126.7 (CH), 143.4 (C3a), 152.5 (C7a); IR (neat) ν: 3385, 3066, 3016, 2954, 2921, 2870, 1478, 1457, 1373, 1046, 1008, 760 cm^{-1}; HRMS-ESI (m/z): 225.1255 $[M+23]^+$ calcd for $C_{14}H_{18}NaO$: 225.1250; Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H; 8.97. Found: C, 82.74; H, 8.88; purity HPLC: 99.6% (Xbridge C8 3.5 μm, 0.4 mL/min, UV 220 nm, acetonitrile/water, 75:25, t_R 3.6 min).

4.1.6. (1R,2S*,9S*)-1,9-Dimethyl-2-(hydroxymethyl)-9-trimethylsilanyl-cyclobuta[1,2-a]indan (**8a**).* To a solution of **6a** (0.94 g, 3.63 mmol, 1 equiv) in THF (40 mL) maintained at −75 °C under an argon atmosphere was added dropwise methyllithium in diethyl ether (1.6 M, 11.4 mL, 18.18 mmol, 5 equiv). The mixture was stirred for 10 min at −75 °C then quenched with a saturated aqueous solution of NH_4Cl and extracted diethyl ether. The organic layers were combined, washed with H_2O, brine then dried (Na_2SO_4), filtered and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane then heptane/dichloromethane, 8:2) to afford 0.96 g (94%) of **8a**, which crystallized on standing: mp 53 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.06 (s, 9H), 0.97 (s, 3H), 1.30 (s, 3H), 1.20 (s, 1H), 1.58 (d, J=12 Hz, 1H), 2.23 (d, J=12 Hz, 1H), 3.13 (d, J=16 Hz, 1H), 3.21 (d, J=16 Hz, 1H), 3.96 (s, 2H), 7.10–7.22 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −1.5 ($3CH_3Si$), 20.8 (C11), 22.0 (C12), 25.0 (C9), 38.4 (C3), 43.1 (C8), 49.6 (C1), 55.0 (C2), 66.3 (C10), 122.6 (CH), 124.0 (CH), 126.6 (CH), 126.7 (CH), 143.6 (C3a), 153.4 (C7a); IR (KBr) ν: 3419, 3067, 3018, 2951, 2923, 2865, 1480, 1458, 1248, 1048, 858, 835, 759 cm^{-1}; HRMS-ESI (m/z): 297.1658 $[M+23]^+$ calcd for $C_{17}H_{26}NaOSi$: 297.1645; Anal. Calcd for $C_{17}H_{26}OSi$: C, 74.39; H; 9.55. Found: C, 74.42; H, 9.51; purity HPLC: 98.4% (Xbridge C18 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 7:3, t_R 12.4 min).

4.1.7. (1R,2S*,9S*)-1,9-Dimethyl-2-(trimethylsilanyloxymethyl)-9-trimethylsilanyl-cyclobuta[1,2-a]indan (**9**).* To a solution of **8a** (0.032 g, 0.116 mmol, 1 equiv) in THF (3 mL) at 0 °C under an argon atmosphere was added potassium bis(trimethylsilyl)amide in toluene (0.5 M, 1.6 mL, 0.58 mmol, 5 equiv). The flask was sealed and the mixture heated in a microwave reactor at 150 °C for 10 min. The mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (silica gel, dichloromethane) to afford 0.005 g of **9**; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.07 (s, 3H), 0.14–0.18 (m, 15H), 0.98 (s, 3H), 1.40 (s, 3H), 1.63 (d, J=12 Hz, 1H), 2.34 (d, J=12 Hz, 1H), 2.60 (d, J=17.4 Hz, 1H), 3.15 (d, J=17.4 Hz, 1H), 3.54 (d, J=10.8 Hz, 1H), 4.00 (d, J=10.8 Hz, 1H), 7.08 (d, J=8 Hz, 1H), 7.12–7.21 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 1.7 (CH_3Si), 1.8 (CH_3Si), 17.3 (C11), 19.5 (C9), 20.7 (C12), 36.8 (C3), 43.2 (C8), 49.0 (C1), 55.4 (C2), 66.1 (C10), 122.4 (CH), 124.3 (CH), 126.5 (CH), 127.1 (CH), 141.6 (C3a), 153.3 (C7a).

4.2. Cyclization of 8a into 6a

To a solution of **8a** (0.052 g, 0.189 mmol, 1 equiv) in THF (5 mL) at 0 °C under an argon atmosphere was added sodium hydride

(0.013 g, 0.568 mmol, 3 equiv). The suspension was stirred at 0 °C for 20 min then at room temperature for 10 min. The flask was sealed and the mixture heated in a microwave reactor at 130 °C for 3 min. The reaction mixture was cooled to 0–5 °C then solid tartaric acid (0.10 g, 0.66 mmol, 3.5 equiv) added in one portion. The mixture was concentrated under reduced pressure, the residue was taken up in heptane, the precipitate formed filtered out on Celite® and the solid washed with heptane. The solvents were removed under reduced pressure and the residue purified by flash column chromatography (neutral alumina, heptane then dichloromethane) to afford 0.036 g (74%) of **6a**.

4.3. Desilylation of 8a with *n*-Bu_4NF

To a solution of **8a** (0.044 g, 0.16 mmol, 1 equiv) in DMF (1.6 mL) under an argon atmosphere was added a solution of tetrabutylammonium fluoride in THF (1 M, 1.6 mL, 1.6 mmol, 10 equiv). The flask was sealed and heated in a microwave reactor at 150 °C for 5 min. The mixture was concentrated under reduced pressure. The residue was taken up in diethyl ether, washed with water, brine then dried (Na_2SO_4), filtered and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, dichloromethane) to afford 0.003 g of **7**.

4.4. Desilylation of 8a with *t*-BuOK

To a solution of **8a** (0.0306 g, 0.114 mmol, 1 equiv) in THF (3 mL) under an argon atmosphere was added at room temperature potassium *tert*-butoxide (0.064 g, 0.57 mmol, 5 equiv) in one portion and the mixture heated in a microwave reactor at 150 °C for 5 min. The THF was evaporated off, the residue was taken up in a saturated solution of NH_4Cl and extracted with diethyl ether. The organic layers were combined, washed with brine then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, dichloromethane) to afford 0.004 g (16%) of **7**.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.07.035.

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