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Synthetic Studies on Cyclobuta[*a*]indanes: Stereocontrolled Access to C9-Substituted Derivatives

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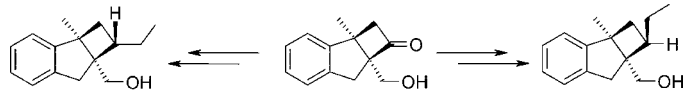
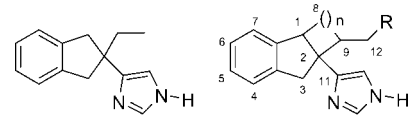


5a 1 5b

We report the preparation of novel ethyl cyclobuta[*a*]indane derivatives of pharmacological interest. The synthesis of compounds **5** was used as a model to study stereocontrolled access to C9-substituted cyclobutane from the corresponding cyclobutanone **1**. Progress was made on two complementary aspects: (1) catalytic hydrogenation from the appropriate cyclobutene precursors; and (2) delivery of the C9 substituent through an intramolecular process. The level of diastereoselectivity obtained through hydrogenation of cyclobutene depends both on the metal used as catalyst and the nature of the functional group proximal to the double bond. The intramolecular delivery approach was diastereospecific, provided that the spiro-intermediate **7** does not ring open during the stereoinduction step. The latter route should allow preparation of quaternary carbon at C9 not available through hydrogenation.

Introduction

There is a long-held theory that noradrenergic mechanisms play a major role in a number of progressive neurodegenerative diseases (e.g., Alzheimer's, Parkinson's).[1] If this is the case, manipulation of such mechanisms should in return interfere with the pathogenic processes and, ultimately, improve treatment outcomes. An effective way to boost noradrenaline levels in the brain is to block presynaptic α_2 receptors which control its release in projection areas.[2] The problem, however, is that there are no selective α_2 antagonists approved for clinical use to test this hypothesis.[3] Further, the interest of the pharmaceutical industry for such an "old" target[4] seems to have faded away. Meanwhile, the incidence of these diseases continues to grow as populations age.[5] Current drugs at best attenuate some of the symptoms but do not slow the progression of these pathologies.[6] In short, therapeutic advances are desperately needed. This prompted us to revisit the field and to take on the challenge of discovering novel α_2 receptors antagonists.



Atipamezole n = 0 or 1

FIGURE 1. Rigid analogues of atipamezole.

Recently, we described a series of benzobicyclo[3.1.0]hexane carbocycles that were potent antagonists at α_2 receptors (Figure 1, $n = 0$).[7] In this case, freezing the conformational flexibility of a known ligand (i.e., atipamezole)[8] perfectly serves our objectives: novelty of the structures and improved pharmacological profile. As a logical continuation, we set out to explore the pharmacological properties of the one-carbon homologue (Figure 1, $n = 1$). Not only does the cyclobutane effectively restrict conformational freedom but also, in the benzobicyclo-[3.2.0]heptane, the contiguous C12−C9−C2−C11 atoms are

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(1) (a) Marien, M. R.; Colpaert, F. C.; Rosenquist, A. C. *Brain Res. Rev.* **2004**, *45*, 38–78. (b) Rizk, P.; Salazar, J.; Raisman-Vozari, R.; Marien, M.; Ruberg, M.; Colpaert, F.; Debeir, T. *Neuropsychopharmacology* **2006**, *31*, 1146–1157. (c) Kalinin, S.; Gavrilyuk, V.; Polak, P. E.; Vasser, R.; Zhao, J.; Heneka, M. T.; Feinstein, D. L. *Neurobiol. Aging* **2007**, *28*, 1206–1214.

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(3) (a) Yohimbine [65-19-0]: Jannini, E. A.; Lenzi, A.; Wagner, G. *Drugs Future* **2003**, *6*, 1165–1172. (b) Mirtazapine [85650-52-8]: Koch, H. *Drugs Future* **1985**, *10*, 965–966, are nonselective α2 antagonists.

(4) The α_2 receptor was among the first GPCR to be cloned: Kobilka, B. K.; Matsui, H.; Kobilka, T. S.; Yang-Feng, T. L.; Francke, U.; Caron, M. G.; Lefkowitz, R. J.; Regan, J. W. *Science* **1987**, *238*, 650–656.

(5) Hodes, R. J. *Nat. Med.* **2006**, *12*, 770–773.

(6) Roberson, E. D.; Mucke, L. *Science* **2006**, *314*, 781–784.

(7) Bonnaud, B.; Funes, P.; Jubault, N.; Vacher, B. *Eur. J. Org. Chem.* **2005**, 3360–3369.

(8) Atipamezole [104054-27-5]: Molderings, G. J. *Drugs Future* **1997**, *22*, 757–772.

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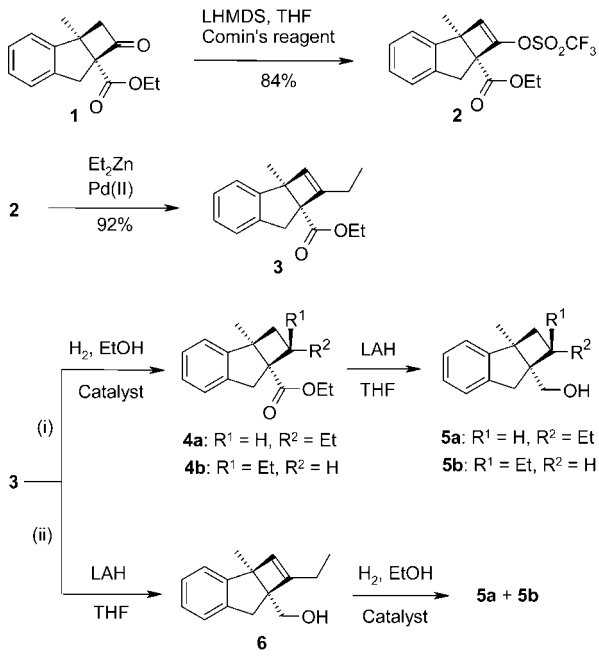
SCHEME 1. Preparation of (±)-5 by Hydrogenation



coplanar and therefore ideally suited for studying the pharmacological impact of the interactions between the groups at C9 and C11 (see Figure 1 for numbering). The whole approach implies, however, that we can control the stereochemistry at C9.

Before our work,[9] polycyclic systems of this type had been rarely documented in the literature.[10] Herein, we present the progress made toward the construction of the model compound **5** using different, complementary routes. Our chemistry efforts focused on methods that would allow access to a range of substituents at C9 for SAR studies and to do so with control over the stereochemistry at this center.

Results and Discussion

Access to a Tertiary Carbon at C9. The most straightforward preparation of compound **5** involves hydrogenation of substrate **3** or **6** (Scheme 1). Both were assembled from the known cyclobutanone **1**.[9] Thus, compound **1** was converted to the ethyl cyclobutene[11] derivative **3** through a Negishi-type coupling[12] between the enol triflate **2** and diethylzinc. Under Hayashi's conditions, **3** was obtained in high yield.[13] Catalytic hydrogenation of the C8−C9 π-bond in **3** proved remarkably versatile in terms of faces differentiation (Scheme 1, path i). Thus, over Pd on activated carbon (Pd/C), the exoethyl isomer **4a** was obtained predominantly (exo/endo = 85:15), whereas changing the catalyst to Adam's (PtO_2) delivered the opposite diastereomer **4b** with even greater selectivity (exo/endo = 6:94). Both reactions were rapid and near-quantitative. Such reversal in stereochemistry when going from Pd to Pt has some precedents in the literature.[14] Subsequent hydride reduction of the ester function led to the corresponding primary alcohols **5**. Unfortunately, the C9 diastereomers were not readily separable by chromatography either at the esters or at the alcohols stages (**4** and **5**, respectively).

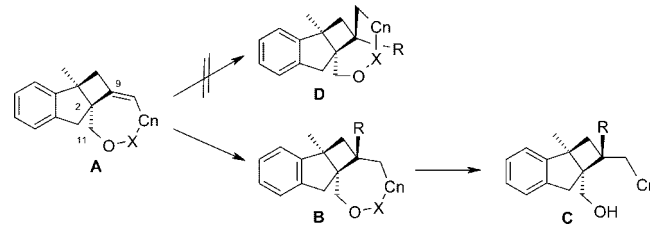


FIGURE 2. An indirect way to control the exostereochemistry at C9.

We also examined hydrogenation from the unsaturated alcohol **6** (Scheme 1, path ii). Interestingly, the stereochemical outcomes were quite different from those observed with **3**. Diastereoselectivity was now complete over Adam's catalyst (**5b** > 98%) but collapsed over Pd/C (**5a**/**5b** = 40:60). Clearly the nature of the functional group at C11 influences the course of the reaction and Pd appears much more sensible than Pt to the local effects of that group. A simple explanation would be that Pt interacts more strongly with the oxygen(s) of the group at C11 than Pd does. Simultaneous coordination of Pt to the oxygen(s) and the double bond then directs hydrogen from the same side as the oxygenated function (exo or *si* face). In contrast, steric effects predominate with Pd so that complexation and hydrogen uptake occurs from the least hindered face of the olefin.

Although this methodology may lead to various alkyl derivatives at C9, depending on the nature of the alkylzinc used in the cross-coupling,[15] the degree of stereoselection ensured in the subsequent reduction step was not entirely satisfactory. We therefore sought a more selective approach that would also encompass the preparation of quaternary carbon at C9.

Stereocontrolled Preparation of Exoethyl Derivative at C9. The hydrogenation tactic implemented above is indeed no longer applicable when C9 is not to bear any hydrogen atom (quaternary). This issue as well as that of enhancing exostereoselectivity at C9 was addressed through the alternative plan outlined in Figure 2. The latter rests on the perception that any transformations performed on the double bond of a spiranic intermediate such as **A** will produce a C9−C2 cis junction in tetracycle **B**; the distortion imposed by a trans ring fusion (cf. **D**) does not appear to be viable except, perhaps, for large spiranic rings. Removal of X in **B** would then release the target **C** in which the incoming group R would be endo- and the resident chain exo-oriented. Indeed, the presence of a bridgehead double bond[16] in **A** introduces another level of strain in these already compressed structures. Concerns regarding stability[17] and feasibility were, however, tempered by the existence of even

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(10) We are aware of only one paper reporting a benzobicyclo[3.2.0]heptane. This compound was obtained as a side product in an electrochemical process: Delaunay, J.; Orliac-Le Moing, A.; Simonet, J.; Toupet, L. *Tetrahedron Lett.* **1986**, *27*, 6205–6208.
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(14) Biswas, S.; Ghosh, A.; Venkateswaran, R. V. *J. Org. Chem.* **1990**, *55*, 3498–3502.
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(16) (a) Bredt, J.; Thouet, H.; Schmitz, J. *Ann.* **1924**, *437*, 1–13. (b) Koebrich, G. *Angew. Chem.* **1973**, *85*, 494–503.

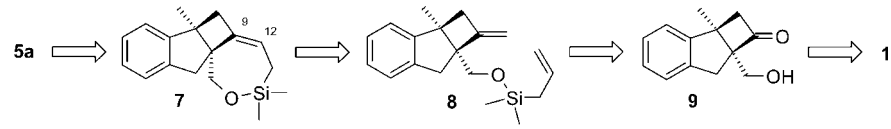


FIGURE 3. Retrosynthesis of **5a**.

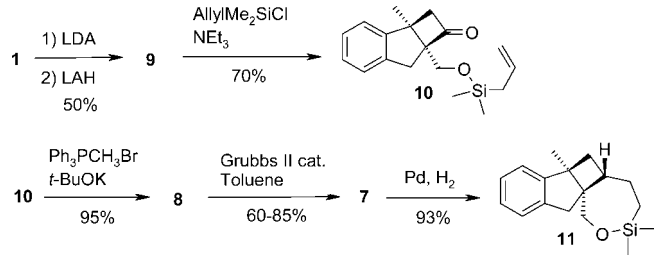
more constrained architectures in products of natural[18] and synthetic[19] origin.

In line with this scenario, we opted for a silicon tether to temporally link C9 and C11 (X = $SiMe_2$ in Figure 2). Application of this strategy to the synthesis of model product **5a** (R = H, $n = 1$ in **C**) is shown in retrosynthetic format in Figure 3. Disconnection across the C9−C12 double bond in **7** uncovered the allylsilylether **8**. The latter could be traced back to the keto alcohol **9** which, in turn, would be derived from known **1**. Although the preparation of **9** from **1** has been partly described earlier (vide infra), we proposed herein a concise alternative.

There are many reports on the formation of siloxacycles of varying size via ring-closure metathesis reaction (RCM).[20,21] Generally, the end game is to control the geometry of the newly created double bond[22] or the configuration at (a) remote stereogenic center(s).[23] Instead, the objective here was to install a π-bond in a thermodynamically disfavored position.[24]

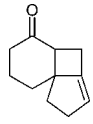
As shown in Scheme 2, the sequence began with the chemoselective reduction of the ester function in **1** to the corresponding primary alcohol while sparing the more reactive ketone at C9. This transformation was best achieved by masking first the ketone as its Li-enolate then reducing the ester group with LAH.[25] Although the yield of **9** was modest (50%), this variant represents a substantial improvement over our previous work,[9] avoiding the need for tedious oxidation level adjustments at C9 and protection−deprotection at C11. Reaction of **9** with dimethylallylchlorosilane[26] followed by Wittig methylenation of the resulting ether (**10**) provided the RCM precursor **8**. When intermediate **8** was subjected to metathesis, using Grubbs's second generation ruthenium as the catalyst (10% loading, 0.007 M), the seven-membered siloxacycle **7** was obtained in 60−85% yields (depending on scale). The newly formed double bond sits in the desired C9−C12 position (no migration was detected)[27] and, indeed, fixed in a *Z*-configuration. With compound **7** in hand, we could then probe the approach highlighted in Figure 2. Further, we anticipated that the relief of the strain stores within the framework of **7** would facilitate any subsequent transformations.

SCHEME 2. Hydrogenation of Intermediate (±)-7



Hydrogenation of the trisubstituted double bond in **7** proceeded under surprisingly mild conditions (room temperature, weak H_2 pressure), revealing how low activation energy this operation required. The geometry of the C9−C2 ring junction in the resulting siloxacycloheptane **11** was exclusively cis.[28] As planned, hydrogen enters from the only accessible endo face of the olefin to deliver **11** as the sole product. From compound **11**, protodesilylation[29] carried out with TBAF in DMF led to the stable silanol **12** (Scheme 3, path i).[30] Although the C−Si bond in **12** resisted all further attempts of protonolysis,[31,32] that

(17) For instance, the compound hereafter was reported to be unstable: Lutteke, G.; AlHussainy, R.; Wrigstedt, P. J.; Buu Hue, B. T.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2008**, 925−933.



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(24) See also: (a) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850–1852. (b) Silver, S.; Leino, R. *Eur. J. Org. Chem.* **2006**, 1965–1977.

(25) (a) Wright, J.; Drtina, G. J.; Roberts, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1988**, *110*, 5806–5817, and references therein. The use of the enol trifluoromethanesulfonate (**2**) to protect the ketone during LAH reduction was unsuccessful; see: (b) Lee, S.-H.; Hulce, M. *Synlett* **1992**, 486–488.

(26) Intramolecular RCM reaction from the vinylsilane analogue of **8** failed to give the corresponding six-membered spirocycle.

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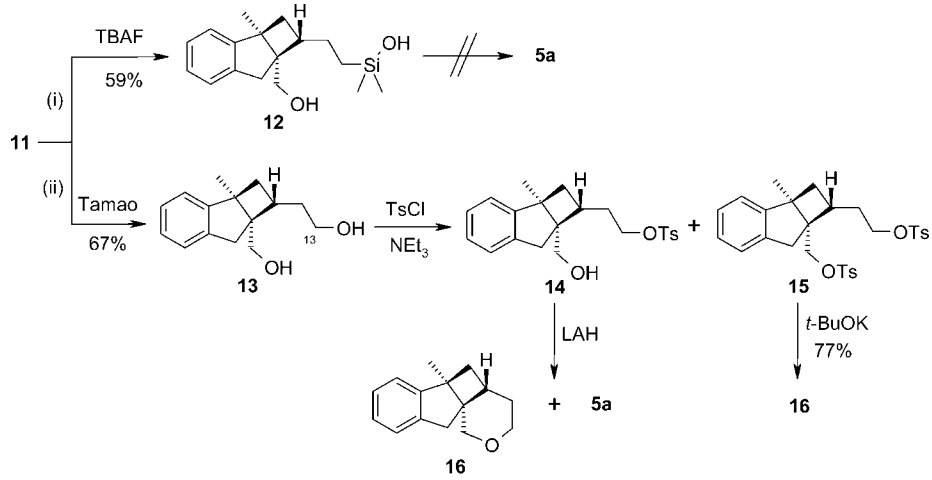
SCHEME 3. Preparation of 5a from 11

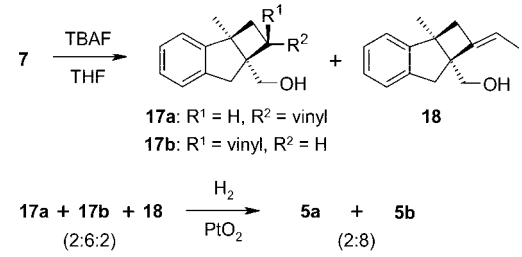


in **11** underwent smooth oxidative cleavage to generate the 1,5-diol **13** (Scheme 3, path ii).[33] Conversion of the OH at C13 to a methyl group then followed a well-established sequence: OH activation−hydride displacement. Thus, tosylation of **13** produced a mixture of the mono- **14** and the ditosylate **15** which were separated by flash chromatography. Treatment of **14** with LAH[34] gave predominantly the tetrahydropyran **16** and only a small amount of the desired derivative **5a** (ca. 9:1, respectively).

On the one hand, the formation of **16** provides direct evidence that the chain at C9 is exo-orientated in **14** (and therefore in compounds upstream). The structure of **16** was secured by means of cyclization from **15**.[35] On the other hand, the facile ring closure of **14**[36] somewhat limits its synthetic utility unless protected at C11. For now, however, isolation of **5a** fulfilled its main objectives: (1) to substantiate the approach set forth in Figure 2; and (2) to ascertain the regiochemistry of the tosylation in **13**.

In order to gain some insight into the reactivity the allylsilane function, we exposed **7** to TBAF in wet THF. Molecular model indicated that conformations where the C13−Si σ-bond and the p-orbitals of the C9−C12 double bond are (nearly) parallel were within reach, underlying that **17a** would prevail. Upon fluoride activation of silicon, **7** afforded a mixture of three compounds (Scheme 4).[37] The major one **17b** (62% crude) arose from allylic transposition[29] but exhibited the counter-expected endovinyl configuration at C9.[38] Such an outcome can only be accounted for if ring opening precedes protonation at the γ-carbon of the allylsilane motif, in which case the stereodirecting effect of the fully annulated system is lost. The other components were the exovinyl derivatives **17a** and the $\Delta^{9,12}$ isomer **18**,[11] the latter

SCHEME 4. Confirmation of the Structures of (±)-17 and 18



presumably stemming from direct C13−Si cleavage in **7**.[39] To support structural characterization, the crude mixture was carried forward into hydrogenation. Thus, treatment of **17a**, **17b**, and **18** (20:62:18 by HPLC) with H_2/PtO_2 yielded **5a** and **5b** (20:80), proportions which are in complete agreement with assignments.

Conclusions

We have explored novel, stereocontrolled routes to potential neuroprotective agents. We thus completed a model study featuring the preparation of 1-methyl-2-(hydroxymethyl)-9-ethylcyclobuta[*a*]indane **5**. A major issue confronted in this series concerned the introduction of substituent(s) at C9 in a stereocontrolled fashion. When C9 is tertiary, we discovered that the 9-endoethyl derivative **5b** can be obtained diastereoisomerically pure by hydrogenation of the cyclobutene precursor **6** over Adam's catalyst. In contrast, the 9-exoethyl isomer **5a** could not be produced with high enough stereochemical purity using this chemistry.

The lack of exoselective method prompted us to develop a conceptually different route that, in addition, may allow the preparation of quaternary carbon at C9. This alternative hinged upon an intramolecular transfer of the desired group from C11 to C9 and used the unsaturated siloxacycle intermediate **7** to relay the stereochemical information. In compound **7**, diastereoselection is ascribed to conformational factors, underlying that the siloxacycle should not ring open before the stereoinduction has taken place.

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(35) The experimental conditions were adapted from: Picard, P.; Leclercq, D.; Moulines, J. *Tetrahedron Lett.* **1975**, *32*, 2731–2732.

(36) On standing at room temperature the monotosylate **14** evolved to **16**.

(37) Varying the temperature of the reaction or using anhydrous TBAF in THF (prepared according to: Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050−2051 did not changed the relative proportions of **17** and **18**.

(38) The endo-stereochemistry in **17b** was initially based on 1D NOESY data: interactions between H9 and H11 indicate that these atoms reside on the same face of the cyclobutane ring (see Supporting Information).

(39) The configuration of the double bond in **18** is based on the assumption that the C9−C12 double bond does not participate in the protonolysis of C13−Si in compound **7**.

We have found that the saturated spiro-intermediate **11** can be channeled toward the diol **13** which, itself, represents a valuable starting point for the synthesis of analogues. Future studies in this series would deal with the construction of a quaternary carbon at C9 and extension to asymmetric approaches.

Experimental Section

(1*S,2*S**)-1-Methyl-2-(ethoxycarbonyl)-9-ethylcyclobut-8-ene-[*a*]indane (3).** To a solution of **2** (1.20 g, 3.22 mmol, 1 equiv) in THF (15 mL) maintained under an argon atmosphere was added dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (261 mg, 0.32 mmol, 0.1 equiv), and the mixture was stirred for 15 min at room temperature. The reaction mixture was cooled to 0 °C then diethylzinc (15 mL, 15 mmol, 1.0 M in toluene, 4.7 equiv) was added dropwise. After the end of the addition, the mixture was heated at 70 °C for 1 h then cooled to room temperature, quenched by slow addition of H_2O, and the aqueous phase was extracted with ethyl acetate. The organic layers were combined, washed with H_2O and brine, then dried (Na_2SO_4), filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane then heptane/ethyl acetate, 9:1) to afford 0.76 g (92%) of **3**: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 1.01 (t, J = 7.4 Hz, 3H, H13), 1.28 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2$), 1.46 (s, 3H, H10), 2.04−2.21 (m, J = 7.4 Hz, 2H, H12), 3.04 (d, J = 17.2 Hz, 1H, H3), 3.55 (d, J = 17.2 Hz, 1H, H3), 4.20−4.26 (m, 2H, $CH_3C\underline{H}_2$), 6.09 (t, J = 2 Hz, 1H, H8), 7.14−7.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 10.1 (C13), 14.4 ($CH_2\underline{C}H_3$), 17.7 (C10), 20.2 (C12), 34.1 (C3), 60.5 ($\underline{C}H_2CH_3$), 62.5 (C1), 62.8 (C2), 122.4 (C7), 126.1 (CH), 126.4 (CH), 127.1 (CH), 137.8 (C8), 142.4 (C3a), 147.3 (C7a), 149.5 (C9), 173.7 (C11); IR (neat) ν 3067, 3037, 2965, 2932, 2873, 1716, 1637, 1456, 1232, 1075, 1050, 757 cm^{-1}; HRMS-ESI (*m*/*z*) 279.1355 $[M + 23]^+$ calcd for $C_{17}H_{20}NaO_2$ 279.1355; purity HPLC 90% (Xbridge C8 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 600:400, t_R 17.4 min).

(1*R,2*S**,9*S**)-1-Methyl-2-(ethoxycarbonyl)-9-ethylcyclobuta-[*a*]indane (4a).** To a solution of **3** (0.50 g, 1.95 mmol) in degassed ethanol (25 mL) was added palladium on activated carbon support (loading 10%, 50 mg). Hydrogen was bubbled through the reaction mixture for 90 min then the content purged with argon and filtered through a pad of Celite. The Celite was washed with ethanol and the solvent removed under reduced pressure to afford 0.48 g (96%) of **4**. The diastereoisomeric purity of **4** was determined by HPLC, **4a/4b** = 85:15.

Compound 4a: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 0.75 (t, J = 7.2 Hz, 3H, H13), 1.33 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2$), 1.36 (s, 3H, H10), 1.42−1.49 (m, 1H), 1.56−1.64 (m, 1H), 2.02−2.31 (m, 3H), 2.93 (d, J = 16.6 Hz, 1H, H3), 3.56 (d, J = 16.6 Hz, 1H, H3), 4.25 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 7.17−7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 11.4 (C13), 14.4 ($CH_2\underline{C}H_3$), 22.9 (C10), 24.0 (C12), 40.3 (C3), 40.8 (C8), 42.0 (C9), 51.5 (C1), 59.6 (C2), 59.9 ($\underline{C}H_2CH_3$), 123.0 (C7), 124.3 (CH), 127.0 (CH), 127.1 (CH), 141.1 (C3a), 150.5 (C7a), 173.4 (C11); IR (neat) ν 3069, 3019, 2958, 2927, 2872, 1720, 1479, 1458, 1263, 1214, 1179, 1036, 760 cm^{-1}; MS-ESI (*m*/*z*) $[M + H]^+$ 259 (100%); HPLC Xbridge C8 5 μm, 1 mL/min, UV 254 nm, acetonitrile/water, 600:400, t_R 25.2 min.

(1*R,2*S**,9*R**)-1-Methyl-2-(ethoxycarbonyl)-9-ethylcyclobuta-[*a*]indane (4b).** To a solution of **3** (0.40 g, 1.57 mmol) in degassed ethanol (25 mL) was added platinum(IV) oxide (40 mg, 0.17 mmol). Hydrogen was bubbled through the reaction mixture for 90 min then the content purged with argon and filtered through a pad of Celite. The Celite was washed with ethanol and the solvent removed under reduced pressure to afford 0.34 g (84%) of **4**. The diastereoisomeric purity of **4** was determined by HPLC, **4a/4b** = 6:94.

Compound 4b: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 0.77 (t, J = 7.6 Hz, 3H, H13), 1.25 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2$), 1.31−1.46 (m, 2H, H12), 1.39 (s, 3H, H10), 1.57 (dd, J = 11.4, 6.4 Hz, 1H, H8), 2.24 (dd, J = 11.4, 1.2 Hz, 1H, H8), 2.96 (m, J = 7.2, 1H, H9), 3.24 (d, J = 17.4 Hz, 1H, H3), 3.53 (d, J = 17.4 Hz, 1H, H3), 4.19 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 7.05−7.22 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 11.6 (C13), 14.4 ($CH_2\underline{C}H_3$), 21.6 (C10), 25.5 (C12), 34.2 (C9), 34.8 (C3), 40.4 (C8), 53.3 (C1), 57.2 (C2), 60.4 ($\underline{C}H_2CH_3$), 122.1 (C7), 124.5 (CH), 126.9 (CH), 127.0 (CH), 143.4 (C3a), 150.3 (C7a), 175.4 (C11); IR (neat) ν: 3069, 3020, 2958, 2929, 2871, 1720, 1481, 1457, 1231, 1188, 1055, 757 cm^{-1}; MS-ESI (*m*/*z*) $[M + H]^+$ 259 (100%); HPLC Xbridge C8 5 μm, 1 mL/min, UV 254 nm, acetonitrile/water, 600:400, t_R 21.7 min.

(1*S,2*S**)-1-Methyl-2-(hydroxymethyl)-9-ethylcyclobut-8-ene-[*a*]indane (6).** To a solution of LAH (10.9 mL, 1.0 M in THF, 10.9 mmol, 1.5 equiv) and THF (10 mL) maintained under an argon atmosphere and cooled at −20 °C was added dropwise a solution of **3** (1.94 g, 7.57 mmol, 1 equiv) in THF (10 mL). The reaction mixture was stirred at −20 °C for 90 min then the reaction quenched by successive additions of H_2O (288 μL), NaOH (288 μL, 30% in H_2O), and H_2O (864 μL). The mixture was filtered through Celite, the Celite washed with THF, and the solvent removed under reduced pressure. The residue was taken up in dichloromethane, washed with brine, then dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, dichloromethane then dichloromethane/ethyl acetate, 95:5) to afford 0.92 g (57%) of **6**: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 1.00 (t, J = 7.2 Hz, 3H, H13), 1.49 (s, 3H, H10), 1.96−2.13 (m, J = 7.2 Hz, 2H, H12), 2.89 (d, J = 17.2 Hz, 1H, H3), 2.96 (d, J = 17.2 Hz, 1H, H3), 3.87 (d, J = 10.8 Hz, 1H, H11), 3.90 (d, J = 10.8 Hz, 1H, H11), 6.05 (t, J = 2 Hz, 1H, H8), 7.14−7.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 10.3 (C13), 17.3 (C10), 20.2 (C12), 35.0 (C3), 57.9 (C1), 59.7 (C2), 65.1 (C11), 122.8 (C7), 126.2 (CH), 126.3 (CH), 126.7 (CH), 137.6 (C8), 142.1 (C3a), 148.8 (C9), 151.8 (C7a); IR (neat) ν 3385, 3065, 3028, 2963, 2912, 2836, 1630, 1478, 1457, 1432, 1019, 757 cm^{-1}; HRMS-ESI (*m*/*z*) 237.1301 $[M + 23]^+$ calcd for $C_{15}H_{18}NaO$ 237.1250; purity HPLC 95.6% (Xbridge C18 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 500:500, t_R 14.2 min).

(1*R,2*S**,9*S**)-1-Methyl-2-(hydroxymethyl)-9-ethylcyclobuta-[*a*]indane (5a).** The same procedure as that used for the reduction of the ester **3** in alcohol **6** was used for the reduction of **4a** (0.49 g, 1.89 mmol). Chromatographic purification (silica gel, dichloromethane/ethyl acetate, 95:5) gave 0.21 g (51%) of **5**. Compound **5a** was separated from **5b** by preparative HPLC: Strategy C18 10 μm, acetonitrile/water, 100:900 (pH 4.5, KH_2PO_4 6.8 g·L^{-1}-H_3PO_4).

Compound **5a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 0.76 (t, J = 7.2 Hz, 3H, H13), 1.36 (s, 3H, H10), 1.47 (m, 1H, H12), 1.74 (m, 1H, H12), 1.49 (s, 1H, OH), 1.80 (t, J = 10.4 Hz, 1H, H8exo), 2.01 (m, 1H, H9), 2.25 (dd, J = 10.4, 8.4 Hz, 1H, H8endo), 2.82 (d, J = 16.4 Hz, 1H, H3β), 3.16 (d, J = 16.4 Hz, 1H, H3α), 3.90 (d, J = 11.2 Hz, 1H, H11), 4.03 (d, J = 11.2 Hz, 1H, H11), 7.16−7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 11.9 (C13), 22.1 (C10), 23.5 (C12), 39.9 (C8), 40.9 (C9), 41.4 (C3), 49.3 (C1), 53.1 (C2), 63.0 (C11), 123.5 (C7), 125.3 (CH), 126.6 (CH), 126.7 (CH), 142.1 (C3a), 151.7 (C7a); IR (neat) ν 3385, 3066, 3016, 2954, 2921, 2870, 1478, 1457, 1373, 1046, 1008, 760 cm^{-1}; HRMS-ESI (*m*/*z*) 239.1417 $[M + 23]^+$ calcd for $C_{15}H_{20}NaO$ 239.1406; purity HPLC 98.6% (Xbridge C18 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 500:500, t_R 26.8 min); for COSY and 1D NOESY data on **5a** see Supporting Information.

(1*R,2*S**,9*R**)-1-Methyl-2-(hydroxymethyl)-9-ethylcyclobuta-[*a*]indane (5b).** The same procedure as that used for the reduction of **4a** was used for the reduction of **4b** (0.34 g, 1.32 mmol). Chromatographic purification (silica gel, dichloromethane/ethyl acetate, 95:5) gave 0.17 g (62%) of **5**.

Compound **5b** (from the reduction of **6** over PtO_2): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 0.76 (t, J = 7.2 Hz, 3H, H13), 1.17 (m, 1H, H12), 1.49 (s, 1H, OH), 1.40 (s, 3H, H10), 1.46 (m, 1H, H12), 1.57 (dd, J = 11.6, 6.4 Hz, 1H, H8), 2.06 (m, 1H, H9), 2.19 (t, J = 11.6 Hz, 1H, H8), 3.00 (d, J = 17.2 Hz, 1H, H3), 3.18 (d, J = 17.2 Hz, 1H, H3), 3.78 (m, 2H, H11), 7.08 (d, J = 6.6 Hz, 1H),

7.12−7.19 (m, 2H), 7.22 (d, $J = 6.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 12.1 (C13), 20.5 (C10), 24.5 (C12), 35.6 (C8), 37.3 (C9), 39.5 (C3), 49.1 (C1), 52.5 (C2), 68.0 (C11), 122.2 (C7), 124.4 (CH), 126.4 (CH), 126.6 (CH), 143.4 (C3a), 152.4 (C7a); HRMS-ESI (*m*/*z*) 239.1406 $[M + 23]^+$ calcd for $C_{15}H_{20}NaO$ 239.1406; purity HPLC 93.3% (Xbridge C18 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 500:500, t_R 18.8 min).

(1*S,2*R**)-1-Methyl-2-(hydroxymethyl)cyclobutan-9-one[*a*]indane (9).** A round-bottom flask was charged with diisopropylamine (4.63 mL, 32.7 mmol, 4 equiv) and THF (30 mL) and maintained under an argon atmosphere. This solution was cooled at −72 °C then BuLi (21 mL, 1.6 M in hexane, 33.6 mmol, 4.05 equiv) was added dropwise. The reaction mixture stirred for 5 min at −72 °C, 30 min at −5 °C, then cooled back to −72 °C. To this solution was added **1** (2.0 g, 8.3 mmol, 1 equiv) in THF (20 mL) over 15 min, and the mixture was stirred at −72 °C for 3 h. To this solution was added LAH (6.6 mL, 1 M in THF, 6.6 mmol, 0.8 equiv) then the reaction mixture was stirred at −72 °C for 30 min and quenched by addition of HCl (1 N). The mixture was filtered under vacuum, the organic phase separated, and the aqueous phase extracted with diethylether. 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, dichloromethane/methanol, 8:2) to afford 0.85 g (50%) of **9** as a white solid: mp 72 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 1.74 (s, 3H, H10), 1.88 (s, 1H, OH), 2.88 (d, $J = 16.8$ Hz, 1H, H8), 3.02 (d, $J = 16.8$ Hz, 1H, H8), 3.29 (d, $J = 18$ Hz, 2H, H3), 3.96 (d, $J = 11.4$ Hz, 1H, H11), 4.01 (d, $J = 11.4$ Hz, 1H, H11), 7.16−7.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 19.8 (C10), 36.8 (C3), 46.2 (C1), 61.3 (C8), 61.8 (C11), 75.6 (C2), 123.6 (CH), 124.9 (CH), 127.4 (CH), 127.7 (CH), 140.6 (C3a), 149.2 (C7a), 214.5 (C9); IR (KBr) ν 3444, 3066, 2960, 2925, 1770, 1599, 1479, 1455, 1372, 1154, 1038, 751 cm^{-1}; MS-ESI (*m*/*z*) $[M + Na]^+$ 225 (100%); purity HPLC 96.3% (Xbridge C8 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 600:400, t_R 27.5 min). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H; 6.98. Found: C, 77.20; H, 7.03.

(1*R,2*S**)-1-Methyl-2-(allyldimethylsilyloxymethyl)-9-methylidenecyclobuta[*a*]indane (8).** A round-bottom flask was charged with methyltriphenylphosphonium bromide (5.72 g, 16 mmol, 1.6 equiv) and THF (60 mL) and maintained under an argon atmosphere. *t*-BuOK (2.07 g, 18 mmol, 1.8 equiv) was added by portions at room temperature, the reaction mixture turned bright yellow, and stirring was continued for 2 h and 30 min. To this mixture was added a solution of compound **10** (3.04 g, 10 mmol, 1 equiv) in THF (30 mL) dropwise, and stirring was continued for 2 h at room temperature. The reaction was quenched by addition of ice−water then the mixture extracted with diethylether. The organic layers were combined and washed with brine, then dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 9:1) to afford 2.75 g (95%) of **8**: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 0.0 (s, 6H), 1.31 (s, 3H, H10), 1.51 (d, $J = 8.0$ Hz, 2H, H13), 2.47 (d, $J = 14.3$ Hz, 1H, H8), 2.71 (dt, $J = 14.3$, 2.4 Hz, 1H, H8), 2.81 (d, $J = 16.0$ Hz, 1H, H3), 3.05 (d, $J = 16.0$ Hz, 1H, H3), 3.64 (d, $J = 10.2$ Hz, 1H, H11), 3.77 (d, $J = 10.2$ Hz, 1H, H11), 4.67 (t, $J = 2.0$ Hz, 1H, H12), 4.75 (s, 1H, H15), 4.76 (d, $J = 26.8$ Hz, 1H, H15), 4.85 (t, $J = 2.4$ Hz, 1H, H12), 5.68 (m, $J = 26.8$, 18.0, 8.0 Hz, 1H, H14), 7.01−7.11 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) −2.6 (CH_3), −2.5 (CH_3), 20.8 (C10), 24.5 (C13), 40.5 (C8), 45.2 (C3), 50.3 (C1), 60.0 (C2), 64.1 (C11), 107.3 (C12), 113.6 (C15), 123.5 (CH), 125.0 (CH), 126.7 (CH), 126.8 (CH), 134.2 (C14), 142.5 (C3a), 151.1 (C7a), 152.4 (C9); IR (neat) ν 3070, 2951, 2907, 2849, 1673, 1630, 1480, 1253, 1075, 866, 757 cm^{-1}; MS-ESI (*m*/*z*) $[M + H]^+$ 299 (100%); purity HPLC 97.5% (Xbridge C8 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 700:300, t_R 24.16 min).

(1*R,2*R**)-1-Methyl-1,9-methano-[2-(1′-oxa-2′,2′-dimethylsilacyclohept-9-ene)]-spiro-2-indane (7).** A round-bottom flask was charged with **8** (0.59 g, 2 mmol, 1 equiv) and degassed toluene (300 mL) and maintained under an argon atmosphere. Grubbs catalyst second generation (170 mg, 0.2 mmol, 0.1 equiv) was added, and the reaction mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, heptane/dichloromethane, 1:1) to afford 0.46 g (85%) of **7**: mp 37−38 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 0.16 (s, 3H), 0.22 (s, 3H), 1.15 (dd, $J = 15.6$, 9.6 Hz, 1H, H13), 1.37 (s, 3H, H10), 1.87 (dm, $J = 15.6$, 4.0 Hz, 1H, H13), 2.59 (dt, $J = 15.6$, 5.2 Hz, 1H, H8), 2.80 (dt, $J = 15.6$, 4.0 Hz, 1H, H8), 3.24 (d, $J = 17.2$, 1H, H3), 3.52 (d, $J = 17.2$, 1H, H3), 3.72 (d, $J = 10.8$, 1H, H11), 4.22 (d, $J = 10.8$, 1H, H11), 5.37−5.41 (m, 1H, H12), 7.16−7.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) −3.3 ($2CH_3$), 19.0 (C13), 20.4 (C10), 41.3 (C8), 44.9 (C3), 49.3 (C1), 59.9 (C2), 68.5 (C11), 120.1 (C12), 123.4 (CH), 125.7 (CH), 127.4 (CH), 127.5 (CH), 142.9 (C3a), 143.2 (C9), 151.3 (C7a); IR (KBr) ν 2954, 2900, 2856, 1476, 1245, 1073, 850, 788, 757 cm^{-1}; HRMS-ESI (*m*/*z*) 311.1448 $[M + 23 + 18]^+$ calcd for $C_{17}H_{24}NaO_2Si$ 311.1438; purity HPLC 99.4% (Xbridge C8 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 500:500, t_R 12.46 min). Anal. Calcd for $C_{17}H_{22}OSi$: C, 75.50; H; 8.20. Found: C, 75.32; H, 8.20.

(1*R,2*S**,9*R**)-1-Methyl-1,9-methano-[2-(1′-oxa-2′,2′-dimethylsilacycloheptane)]-spiro-2-indane (11).** To a solution of **7** (0.15 g, 0.55 mmol) in degassed ethyl acetate (15 mL) was added palladium on activated carbon support (loading 10%, 21 mg). Hydrogen was bubbled through the reaction mixture for 2 h, then the content was purged with argon and filtered through a pad of Celite, concentrated, then filtered through Florisil, eluting with ethyl acetate. The solvent was removed under reduced pressure to afford 0.39 g (93%) of **11**: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 0.17 (s, 3H), 0.22 (s, 3H), 0.58 (t, $J = 14.0$ Hz, 1H, H13), 0.70 (dd, $J = 14.0$, 8.4 Hz, 1H, H13), 1.20 (s, 3H, H10), 1.69−1.77 (m, 2H, H12+H8), 1.85−1.88 (m, 1H, H12), 2.09−2.17 (m, 1H, H9), 2.17 (t, $J = 8.4$ Hz, 1H, H8), 2.95 (d, $J = 16.8$, 1H, H3β), 3.19 (d, $J = 16.8$, 1H, H3α), 3.67 (d, $J = 11.6$, 1H, H11β), 4.31 (d, $J = 11.6$, 1H, H11α), 7.17−7.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) −2.9 ($2CH_3$), 16.1 (C13), 21.4 (C10), 26.5 (C12), 41.2 (C8), 41.6 (C9), 45.0 (C3), 48.2 (C1), 54.0 (C2), 63.9 (C11), 123.4 (CH), 125.2 (CH), 126.7 (CH), 126.8 (CH), 142.1 (C3a), 152.0 (C7a); IR (neat) ν 2953, 2902, 2855, 1479, 1250, 1089, 852 cm^{-1}; HRMS-ESI (*m*/*z*) 313.1598 $[M + 23 + 18]^+$ calcd for $C_{17}H_{26}NaO_2Si$ 313.1594; purity HPLC 91% (Uptisphere C4 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 800:200, t_R 8.45 min).

(1*R,2*S**,9*R**)-1-Methyl-2-(hydroxymethyl)-9-[2-(hydroxydimethylsilyl)ethyl]cyclobuta[*a*]indane (12).** A round-bottom flask was charged with **11** (294 mg, 1.0 mmol, 1 equiv) and DMF (11 mL) and maintained under argon atmosphere. To this stirred solution was added tetrabutylammonium fluoride (10 mL, 1 M in THF, 10 mmol, 10 equiv) at room temperature, and the mixture was stirred for 24 h. The solvents were removed under reduced pressure. The residue was taken up in diethylether and washed with H_2O and brine, then dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, dichloromethane/methanol, 95:5) to afford 171 mg (59%) of **12**: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 0.10 (s, 6H), 0.39 (m, 1H, H13), 0.50 (m, 1H, H13), 1.23 (s, 3H, H10), 1.34−1.42 (m, 1H, H12), 1.65−1.75 (m, 2H, H12+H8), 1.96 (c, $J = 8.4$ Hz, 1H, H9), 2.14 (dd, $J = 10.8$, 8.4 Hz, 1H, H8), 2.39 (s, 1H, OH), 2.89 (d, $J = 16.4$ Hz, 1H, H3β), 3.13 (d, $J = 16.4$ Hz, 1H, H3α), 3.85 (d, $J = 11.2$ Hz, 1H, H11β), 4.09 (d, $J = 11.2$ Hz, 1H, H11α), 7.16−7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) −0.55 (CH_3), −0.17 (CH_3), 15.5 (C13), 21.9 (C10), 24.0 (C12), 39.9 (C8), 42.0 (C3), 42.2 (C9), 49.1 (C1), 53.2 (C2), 63.1 (C11), 123.5 (CH), 125.3 (CH), 126.6 (CH), 126.7 (CH), 142.1 (C3a), 151.7 (C7a); IR (neat) ν 3357, 2952, 2919, 1479, 1265, 1021, 841 cm^{-1}; HRMS-ESI (*m*/*z*) 313.1608 $[M + 23]^+$ calcd for $C_{17}H_{26}NaO_2Si$ 313.1594; purity HPLC 95.1% (Uptisphere C4 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 600:400, t_R 7.72 min).

(1*R,2*S**,9*R**)-1-Methyl-2-(hydroxymethyl)-9-(2-hydroxyethyl)cyclobuta[*a*]indane (13).** To a solution of **11** (298 mg, 1.09 mmol, 1 equiv) in DMF (50 mL) were added successively KF (197 mg, 3.39 mmol, 3 equiv) and H_2O_2 (2.4 mL, 30% H_2O_2 in H_2O, 21 mmol, 20 equiv). The mixture stirred at room temperature for 12 h, at 70 °C for 90 min, then cooled to room temperature and brine was added. The mixture was extracted with diethylether, the organic layers were combined and washed with brine then dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 8:2 then ethyl acetate) to afford 169 mg (67%) of **13**: mp 78 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 1.13 (s, 3H, H10), 1.48−1.54 (m, 1H, H9), 1.77 (t, J = 10.0 Hz, 1H, H8), 1.97−2.08 (m, 2H, H12), 2.14 (dd, J = 10.4, 7.6 Hz, 1H, H8), 3.01 (d, J = 16.4 Hz, 1H, H3), 3.19 (s, 2H, OH), 3.09 (d, J = 16.4 Hz, 1H, H3), 3.45−3.51 (m, 1H, H13), 3.67 (d, J = 11.2 Hz, 1H, H11), 3.72−3.77 (m, 1H, H13), 4.24 (d, J = 11.2 Hz, 1H, H11), 7.16−7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 21.5 (C10), 33.1 (C8), 37.9 (C9), 40.0 (C12), 42.1 (C3), 49.8 (C1), 53.8 (C2), 62.7 (C13), 63.0 (C11), 123.5 (CH), 125.4 (CH), 126.7 (CH), 126.8 (CH), 142.3 (C3a), 151.4 (C7a); IR (KBr) ν 3299, 2920, 2862, 1478, 1029, 760 cm^{-1}; HRMS-ESI (*m*/*z*) 255.1370 $[M + 23]^+$ calcd for $C_{15}H_{20}NaO_2$ 255.1356; purity HPLC 98.4% (Xbridge C8 5 μm, 1 mL/min, UV 220 nm, acetonitrile/water, 400:600, t_R 6.81 min). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.29; H, 8.82.

(1*R,2*S**,9*R**)-1-Methyl-2-(hydroxymethyl)-9-[2-(*p*-toluenesulfonyloxy)ethyl]cyclobuta[*a*]indane (14).** To a solution of **13** (113 mg, 0.48 mmol, 1 equiv) in dichloromethane (4 mL) cooled at 0 °C and maintained under an argon atmosphere were added successively triethylamine (0.149 mL, 1.07 mmol, 2.2 equiv) and a catalytic quantity of 4-dimethylaminopyridine. To this solution was added *p*-toluenesulfonylchloride (186 mg, 0.97 mmol, 2 equiv), and the mixture was stirred at 0 °C for 1 h then the temperature was allowed to reach room temperature. The reaction mixture was concentrated down and the residue taken up in ethyl acetate, washed with dilute hydrochloric acid, water, and brine, then dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate, 8:2 then ethyl acetate) to afford 144 mg (57%) of **14**: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 1.20 (s, 3H, H10), 1.73 (m, 1H, H9), 1.94−2.14 (m, 3H, 2H12+H8), 2.43 (s, 3H), 2.53 (m, 2H, H8+OH), 2.73 (d, J = 16.0 Hz, 1H, H3), 3.02 (d, J = 16.0 Hz, 1H, H3), 3.75−4.00 (m, 2H, H13), 3.83 (d, J = 10.8 Hz, 1H, H11), 4.01 (d, J = 10.8 Hz, 1H, H11), 7.12 (d, J = 7.6 Hz, 1H), 7.21 (m, 3H), 7.26 (d, J = 7.6 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 21.6 (CH_3), 21.8 (C10), 30.1 (C8), 35.3 (C9), 39.7 (C12), 41.6 (C3), 49.8 (C1), 53.2 (C2), 63.1 (C11), 69.5 (C13), 123.3 (CH), 125.5 (CH), 126.8 (CH), 126.9 (CH), 127.8 (2CH), 129.8 (2CH), 133.0 (Cq), 141.6 (C3a), 144.6 (Cq), 150.1 (C7a); MS-ESI (*m*/*z*) $[M + Na]^+$ 409 (46%), $[M + NH_4]^+$ 404 (97%), 369 (70%), 197 (100%); HPLC Xbridge C18 5 μm, 1 mL/min, UV 254 nm, acetonitrile/water, 500:500, t_R 27.0min.

(1*R,2*S**,9*R**)-1-Methyl-2-(*p*-toluenesulfonyloxy)-9-[2-(*p*-toluenesulfonyloxy)ethyl]cyclobuta[*a*]indane (15).** Purification of **14** afforded 20 mg (8%) of **15**: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 1.18 (s, 3H, H10), 1.43 (m, 1H, H9), 1.67 (t, J = 10.4 Hz, 1H, H8), 1.87−2.14 (m, 3H, 2H12+H8), 2.43 (s, 3H), 2.46 (s, 3H), 2.72 (d, J = 16.4 Hz, 1H, H3), 2.85 (d, J = 16.4 Hz, 1H, H3), 3.75−3.85 (m, 1H, H13), 3.80−3.90 (m, 1H, H13), 4.12 (d, J = 9.6 Hz, 1H, H11), 4.34 (d, J = 9.6 Hz, 1H, H11), 7.08 (d, J = 8.0 Hz, 1H), 7.10−7.21 (m, 3H), 7.26 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 7.6 Hz, 2H), 7.79 (d, 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 21.6 ($2CH_3$), 21.9 (C10), 29.8 (C8), 37.4 (C9), 39.6 (C12), 41.7 (C3), 50.2 (C1), 51.3 (C2), 68.8 (C11), 70.7 (C13), 123.4 (CH), 125.3 (CH), 127.1 (CH), 127.2 (CH), 127.8 (2CH), 127.9 (2CH), 129.8 (2CH), 130.0 (2CH), 132.6 (Cq), 132.9 (Cq), 140.9 (C3a), 144.7 (Cq), 145.1 (Cq), 150.1 (C7a); IR (neat) ν 2949, 2921, 1357, 1175, 665 cm^{-1}; MS-ESI (*m*/*z*) $[M + Na]^+$ 563 (24%), $[M + NH_4]^+$ 558 (60%), 369 (100%).

(1*R,2*S**,9*R**)-1-Methyl-1,9-methano-[2-(3-oxacyclohexane)]spiro-2-indane (16).** To a solution of **15** (38 mg, 0.096 mmol, 1 equiv) in DMSO (3 mL) stirred at room temperature was added *t*-BuOK (34.4 mg, 0.30 mmol, 3 equiv), and stirring was continued for 8 h. The reaction mixture was poured into a saturated NH_4Cl aqueous solution and extracted with diethylether. The organic layers were combined and washed with H_2O and brine, then dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, dichloromethane) to afford 16 mg (77%) of **16**: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 1.31 (s, 3H, H10), 1.83−1.94 (m, 2H), 2.04−2.18 (m, 3H), 2.74 (d, J = 16.4 Hz, 1H, H3), 2.92 (d, J = 16.4 Hz, 1H, H3), 3.73−3.89 (m, 2H, H13), 3.80 (d, J = 12.4 Hz, 1H, H11), 3.97 (d, J = 12.4 Hz, 1H, H11), 7.16−7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 21.7 (C10), 23.9 (C8), 30.9 (C9), 37.4 (C12), 42.5 (C3), 47.4 (C1), 50.6 (C2), 63.6 (C13), 69.0 (C11), 123.8 (CH), 125.3 (CH), 126.7 (CH), 126.9 (CH), 142.0 (C3a), 151.7 (C7a); IR (neat) ν 2949, 2910, 1714, 1275, 1178, 1111, 755 cm^{-1}; HRMS-ESI (*m*/*z*) 255.1361 $[M + H_2O + 23]^+$ calcd for $C_{15}H_{20}NaO_2$ 255.1355; HPLC Xbridge C18 5 μm, 1 mL/min, UV 254 nm, acetonitrile/water, 500:500, t_R 26.3 min.

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Supporting Information Available: . ^{1}H and ^{13}C NMR spectra of new compounds and experimental procedures for compounds **2**, **10**, **17b**, **17a**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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