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Preparation of Conformationally Constrained α_2-Antagonists: The Bicyclo[3.2.0]heptane Approach

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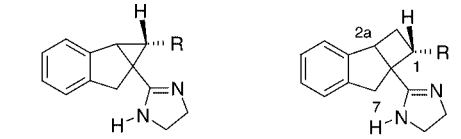
The aim of this research was to discover α_2-receptor antagonist subtypes that are more selective than known compounds. We focused on rigid molecules possessing a benzo-fused bicyclo[3.2.0]heptane skeleton. The synthetic route used relied upon the intramolecular [2+2] cycloaddition of styrylketene precursors. The cycloaddition was remarkably efficient and delivered multigram quantities of the cycloadduct **2**. Studies of the removal of the ketone group in **2** revealed a facile opening of the four-membered ring. Upon thermal elimination of TCI-**13**-*endo* (TCI = thiocarbonylimidazole) and TCI-**13**-*exo*, different products were obtained depending on the stereochemistry of the OH function of the precursor. Distinct mechanisms were proposed to account for the divergent outcomes observed. Double bond reductions from either methylcyclobutene or methylenecyclobutane isomers were thoroughly investigated in order to optimize the stereocontrol at the C-1 position. Hydrogenation of the internal π-bond produced an *endo*-1-methylcyclobutane derivative with high diastereoselectivity, whereas the *exo*-1-methyl isomer was best isolated by chromatographic separation of the acid **37**. Finally, the prototypic imidazolidines **1**, unsubstituted and bearing a methyl group at C-1, were synthesized for biological evaluation.

Introduction

Over the last few years, we have taken part in research aimed at discovering antagonists at the α_2-receptors that are more subtype-selective than known compounds. At present, the role of the individual subtype remains largely conjecture. Initially, we focused on cyclopropyl analogues of atipamezole, and reported on the derivatives of the type bicyclo[3.1.0]hexane (Figure 1).[1a] Such compounds, in particular those bearing a 2-imidazoline pharmacophore, exhibit improved selectivity at the α_{2A}-sites compared to the α_{2B}- and α_{2C}-sites.[1b] Pursuing this promising vein, we have now extended our investigations to include derivatives of the bicyclo[3.2.0]heptane type, homologues of the compounds described previously. Thus, this paper deals with the syntheses of compounds of type **1** (Figure 1) which contain a cyclobutyl ring instead of a cyclopropyl ring in their skeleton.[1c]

The conformational mobility of the bicyclo[3.2.0]heptane, like that of their bicyclo[3.1.0]hexane relatives, is completely abolished by ring fusion with the benzene nucleus. Hence, the three-dimensional structures of the carbocycles in **1** are perfectly defined.

The bicyclo[3.2.0]heptane system is commonly derived from an intermolecular [2+2] cycloaddition between an indene-type substrate and a dichloroketene,[2] or another ketene equivalent.[3] Herein, we report a novel approach to the key benzo-fused bicyclo[3.2.0]heptane intermediates **2** (Scheme 1), and disclose our full synthetic studies towards the prototypic molecules **1**, in which R = H and R = CH_3 (Figure 1).[4]



Bicyclo[3.1.0]hexane series **1**

Figure 1. Structure of the bicyclo[3.2.0]heptanes **1** under study.

Results and Discussion

Synthesis of Cyclobutanone Key Intermediates

We anticipated that compound **1** could arise from an intramolecular [2+2] cycloaddition between a benzylic ketene and an *ortho*-styryl double bond (Scheme 1).

According to this plan, functional group interconversion at C-1 and C-7a led to the cyclobutanone **2** which, in turn, was disconnected to form the styrylketene **3** (Scheme 1). A few considerations influenced our choice for an intramolecular rather than a classic intermolecular ketene cycloaddition: 1) we found no example of an intermolecular process taking place with a 2,3-disubstituted indene double bond,[5a] 2) stereoelectronic effects[5b,6] predict a preference

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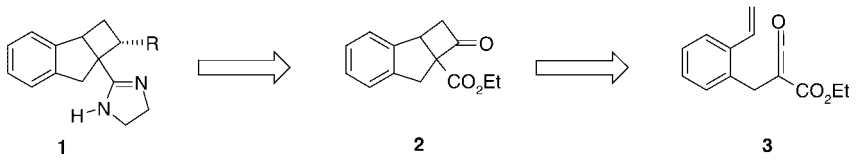
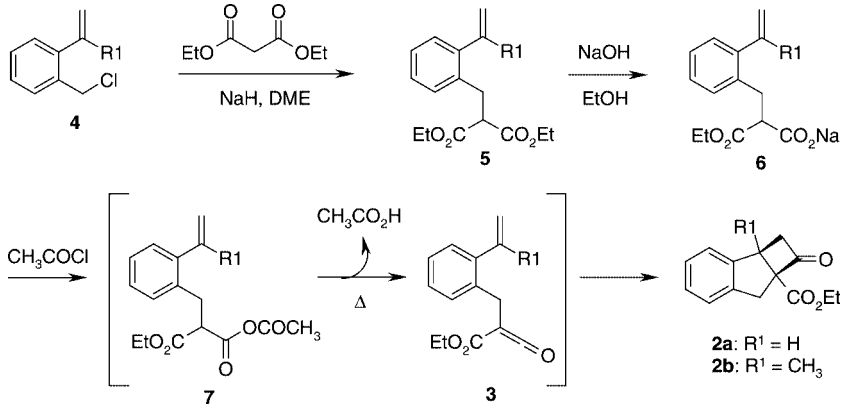


Scheme 1. Retrosynthetic analysis of compounds of type **1**.



Scheme 2. Synthesis of the building blocks **2**.

for the [3.2.0] adduct (**2**) as opposed to the [3.1.1] regioisomer in the cycloaddition of **3**[6] and 3) although cyclizations of aryloxy-[7] or azastyrylketenes[8] are known methods for obtaining benzofurans or indole-fused cyclobutanones, the equivalent reaction has not been, thus far, applied to the "all-carbon" series.[9] We believed that filling such a gap would therefore be a useful contribution.

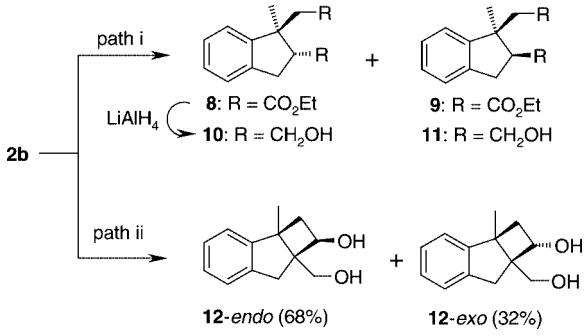
The synthetic route to the key intermediates **2** is summarized in Scheme 2.

Chain extension of styrene **4**[1a] with diethyl malonate afforded the diester **5**. Saponification and treatment of the monosodium salt **6** with acetyl chloride provided the mixed anhydride **7** which was utilized directly in the next step. Thermal elimination of acetic acid produced the transient ketene **3** which was trapped intramolecularly by the styrene double bond to give the cyclobutanone **2**. The regioisomeric bicyclo[3.1.1]heptanone was not detected in the cycloaddition. In our hands, this method of generating the ketene[10] **3** is far more efficient than those which rely upon base-induced eliminations.[11]

However, the cycloaddition of **3a** (R^1 = H) performed poorly (<30%) and unreliably; these results are consistent with literature observations of a related system.[12] In addition, the adduct **2a** proved to be unstable and decomposed within a few days after isolation. In sharp contrast, the substituted styrene **3b** (R^1 = CH_3) underwent cycloaddition in good yield (>70%) and delivered the stable synthon **2b**. The latter was therefore selected as a platform for launching further studies; the adjunction of a methyl group at this position in the cyclopropane series had no significant influence on the biological activity.

Access to 1-Unsubstituted Cyclobutanes

Utilizing **2b**, attempts to reduce the ketone group chemoselectively, using $NaBH_4$ or $LiBH_4$, led exclusively to the disubstituted indans **8**, **9** and **10**, **11**, respectively (Scheme 3, path i).[13]



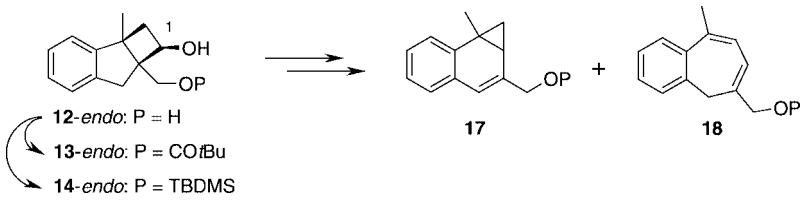
Scheme 3. Attempts at reduction of the intermediate **2b**.

This facile ring-opening of cyclobutanone **2b** stood as a serious obstacle.[14] Obviously, the retro-Dieckmann reaction, already favored entropically, was further encouraged by releasing the strain built up in the structure.[15] The underlying message was clear: to preserve the cyclobutane ring one needed to disarm the 1,3-dicarbonyl system first.

A solution to this problem arose in a rather unexpected way.[16] Thus, treatment of **2b** with $LiAlH_4$ (Scheme 3, path ii) yielded the 1,3-diols **12** exclusively.[17] The absence of any ring-opened by-product under these conditions indicated that the reduction of the ester preceded that of the ketone, a somewhat counterintuitive finding. At this juncture, the lack of stereoselectivity in the reduction step was considered of no practical consequence;[18] an assumption that later proved to be not entirely valid (vide infra).

In any case, to reach unsubstituted cyclobutanes of type **1** we needed to remove the redundant hydroxy group at C-1. This task turned out to be particularly challenging using the major *endo* isomer **12** (cf. Scheme 3, path ii).

Out of the methods surveyed to remove the secondary OH group from **13**-*endo* or **14**-*endo*, only the thermal elimi-



Scheme 4. Attempts at deoxygenation of **12**-*endo*.

nations of the thiocarbonylimidazolide (TCI) produced exploitable results (compounds **17** and/or **18**, Scheme 4).[19] The formation of these rearranged isomeric products was rationalized by the mechanisms depicted in Figure 2.

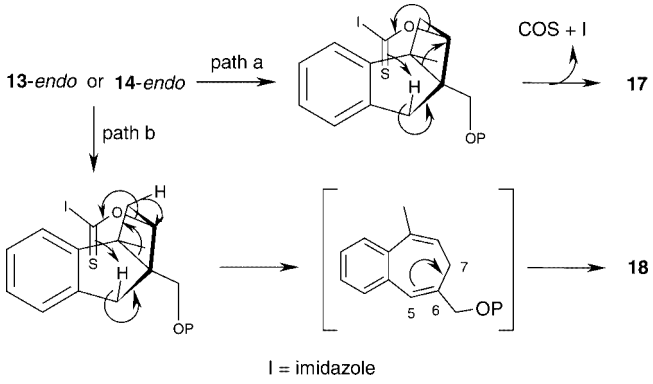


Figure 2. Mechanistic considerations of the formation of by-products **17** and **18**.

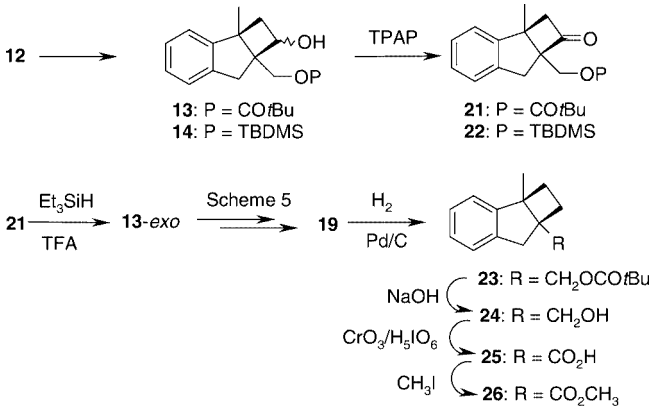
Because **17** and **18** were not interconvertable, we assumed that they originated from different, possibly competing, mechanisms. We propose that the pyrolytic rearrangement of an *endo*-TCI is triggered by the attack of the TCI on the more remote γ-hydrogen atom, instead of the *syn*-β-hydrogen atom, as would be expected from a classic E_i mechanism. Such a 7-centered interaction would minimize steric repulsions between the TCI and the indane moieties. The outcome of the reaction depends upon the fate of the breaking of the C-2a–C-7a σ-bond: migration of this bond to the C-1–C-2a position would generate **17** (Figure 2, path a), whereas a 1,2-shift of a hydrogen atom would lead to diene **18**, after isomerization of the 5,6-double bond (path b). Paths a and b should have different activation barriers which impose energetic control over the course of the reaction.

We realized however, that if these mechanistic hypotheses are correct, the desired E_i mechanism would be possible, provided it was conducted on an *exo*-TCI. Unlike *endo*-TCIs, *exo*-TCIs have a *syn*-β-hydrogen atom well within thermodynamic reach. Such a possibility prompted us to re-examine the thermal elimination but, this time, from the minor isomer **12**-*exo* (Scheme 5).

Thus, heating of the TCI derivatives **15**-*exo* or **16**-*exo* furnished the cyclobutenes **19** or **20** as the sole products in yields exceeding 70%, whatever the nature of the protecting group.[20] These results have important implications: (1) they lend support to the mechanisms claimed in Figure 2; (2) the stability of the fused cyclobutene has been ascertained[21] and (3) a stereoselective synthesis of **12**-*exo* is mandatory for access to **1** in a practical way.

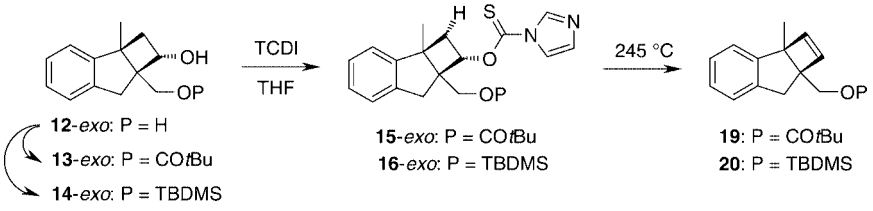
Ironically, solving the deoxygenation problem raised the issue of devising a stereoselective route to **12**-*exo* (or a protected derivative of it). This was a matter of some concern, since the reduction of the C-1 ketone by a metal hydride gave predominantly the wrong *endo* stereoisomer, whatever the substrates used (i.e., **21**, **22** or **42**).[22a]

An indirect but stereoselective route to **13**-*exo* was eventually worked out and is summarized in Scheme 6.



Scheme 6. A stereoselective route to **13**-*exo*, a key intermediate of **26**.

The mixture of diols (**12**-*endo*/*exo* = 68:32), straight from the $LiAlH_4$ reduction of **2b** (Scheme 3, path ii), was monoprotected (CO*t*Bu or TBDMS) and, without purification, ox-

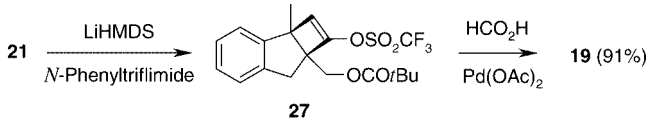


Scheme 5. Pyrolytic eliminations performed on derivatives of **12**-*exo*.

idized back to the cyclobutanone **21** or **22** (TPAP/NMO).[23]

The salient feature of this maneuver rests upon the total *exo* diastereoselectivity of the hydrosilane reduction of the ketone **21**.[22b] Such facial discrimination, opposite to that seen with metal hydrides, is ascribed to the anchimeric participation of the pivalate group, which generates an oxocarbenium species, forcing the hydride ion to attack from the *endo* direction. Once the correct *exo* stereochemistry at C-1 was secured, thermolysis could be carried out as before (Scheme 5). Using olefin **19**, hydrogenation of the π-bond led to the cyclobutane **23**. Next, the oxidation state of the chain at C-7a was adjusted to form acid **25**, subsequent esterification provided **26** ready for conversion to a 2-imidazoline group.

This sequence, though by no means optimal, has the merit of supplying enough material to enable progress towards **1**. Subsequently, we developed a synthesis of the cyclobutene **19** not limited by the availability of a derivative having an *exo*-OH group at C-1 (cf. Scheme 7).

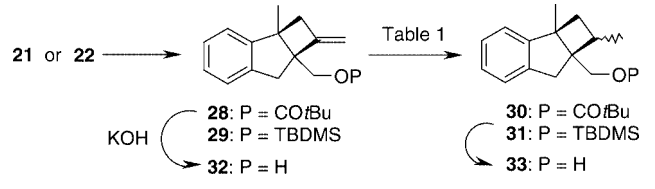


Scheme 7. A more concise route to compound **19**.

The stable enol triflate **27** was first prepared in 65% yield from the ketone **21**.[24] Direct access to the fully reduced material **23** is indeed possible from **27**,[25] however, in view of the synthetic potential of the cyclobutene **19** we chose to isolate it. Hydrogenolysis of the triflate bond in **27**, according to a literature protocol,[24] allowed this conversion to be performed efficiently.

Access to *exo*-1-Methylcyclobutanes

Intermediates **21** and **22** also served as starting points for the synthesis of the 1-substituted cyclobutanes (Scheme 8). Initially, the extra carbon atom at C-1 was introduced by Wittig chemistry.



Scheme 8. 1-Substituted cyclobutanes based on Wittig chemistry.

Accordingly, the ketones **21** and **22** underwent standard Wittig olefination to afford the *exo*-methylene derivatives **28** and **29**, respectively. Reduction of the double bond then afforded the corresponding saturated intermediates **30** and **31**. Mixtures of epimers at C-1 were always obtained which, moreover, were not amenable to chromatographic separation neither at the stage of the protected alcohols (**30** or **31**) nor later (vide infra).[26] Hence, the stereoselectivity issue became critical enough for us to study the reduction process in some depth (cf. Table 1).

Table 1. Diastereoselectivity of the hydrogenation of methylenecyclobutane derivatives.

Entry	Substrate	Catalyst	Solvent	*T* [°C]	Product (*exo*/*endo*)[a]
1	**28**	Pd/C[b]	*n*-heptane	room temp.	**30** (42:58)
2	**28**	Pd/C[b]	EtOAc	room temp.	**30** (43:57)
3	**28**	Pd/C[b]	EtOH	room temp.	**30** (63:37)
4	**28**	Pd/C[b]	AcOH	room temp.	**30** (51:49)
5	**28**	Pd/C	EtOH	–8 °C	**30** (60:40)
6	**28**	Pd/C	EtOH	reflux	**30** (65:35)
7	**28**	PtO_2	EtOH	room temp.	**30** (50:50)
8	**28**	Raney Ni	EtOH	room temp.	no reaction
9	**29**	Pd/C	EtOH	room temp.	**31** (65:35)
10	**32**	Pd/C	EtOH	room temp.	**33** (30:70)

[a] Ratio determined by ^{1}H NMR spectroscopy. [b] 10% Pd/C was used in these reactions.

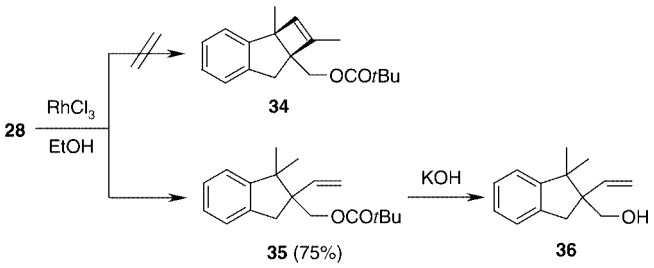
As shown in Table 1, moderate *exo* preference for the 1-methyl group was achieved when using Pd/C in ethanol (Entries 3 or 9), as the bulky protecting group impedes the uptake of hydrogen from the *exo* face of the molecule. Yet, varying the reaction parameters (solvent polarity or temperature, Entries 1–6) did not improve the *exo*/*endo* ratio. On the other hand, changing the nature of the metal was truly detrimental (Entries 7 and 8).[27]

Swapping steps around (i.e., deprotection before hydrogenation) inverted the epimeric ratio of **33** (Entry 10), implying that the free hydroxy group does exert some directing effect;[28] although the gain in selectivity has not attained an exploitable level. Besides, the diimide reduction of **28** or **29** was totally unselective, just like the hydrogenation of **28** under homogeneous catalysis conditions (Wilkinson's catalyst).[29,30]

By now, we were convinced that hydrogenation of **28** (or congeners)[31] could not deliver **30** with the degree of selectivity we would like. Drawing from the hypothesis that the reduction of 1-methylcyclobutene should be more selective than that of 1-methylenecyclobutane, our next objective was to probe the hydrogenation of cyclobutene **34**.

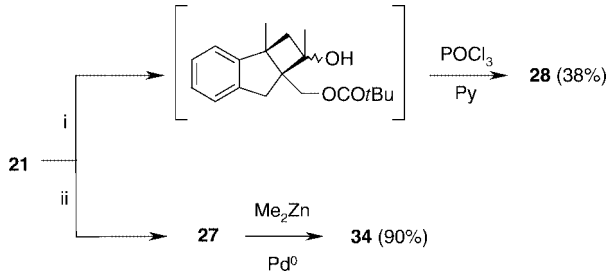
However, when we attempted to prepare **34** by "thermodynamic" isomerization of **28** ($RhCl_3 \cdot 3H_2O$),[32] only the indane **35** was produced (characterized as **36**), Scheme 9. Seemingly, **28** had suffered a net reductive cleavage about the σ(C-1–C-2) bond.[33] Although the divergent behavior of **28** in the presence of Rh^I or Rh^{III} was intriguing, we did not push further in this direction.

Efforts to obtain **34** from **28** being of no avail, we considered other approaches (Scheme 10). Addition of MeMgI to ketone **21** gave a mixture of diastereomeric alcohols in a 6:4 ratio, quantitatively but, upon elimination ($POCl_3$/pyridine), only **28** was isolated in low yield (path i);[27b] small amounts of **34** (<5%) were also detected by ^{1}H NMR of the crude reaction mixture. Since both isomers were consumed in the reaction, we suspect that one of the tertiary alcohol epimers underwent regioselective elimination on the methyl side while the other decomposed under the reaction



Scheme 9. Attempted isomerization of the double bond in **28**.

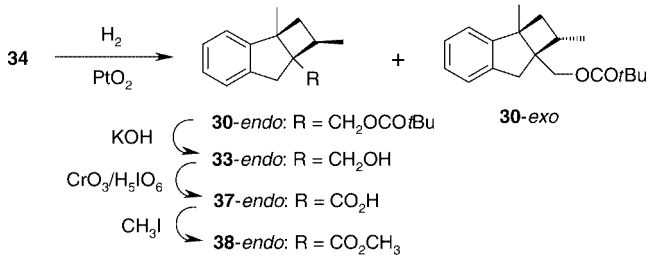
conditions (by analogy with the TCI elimination cases). The enol triflate **27** turned out to be the intermediate of choice for this chemistry (path ii).[34]



Scheme 10. Alternative routes to **34**.

Thus, palladium-catalyzed methylation of **27** produced the much sought-after compound **34** in good yield.[35] As dicussed before, **27** also offered a shorter **13**-*exo*-independent route to the unsubstituted cyclobutene **19** (cf. Scheme 7).[36]

With compound **34** in hand, the response to hydrogenation could be tested (Scheme 11).

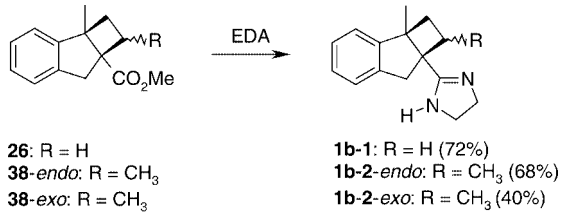


Scheme 11. Diastereoselectivity of the hydrogenation of **34**.

Reduction of **34** using Adam's catalyst occurred with almost complete *endo* diastereoselectivity (*endo*/*exo* > 95:5). This result, although opposite to the desired one, was much welcome as it settled our assignments of **30**-*endo* and its relatives (i.e., **31**-, **33**-, **37**- and **38**-*endo*, Scheme 11 and Table 1).[37] No reaction took place using Pd/C, illustrating the loss in reactivity of the intracyclic π-bond (compared with Entry 5 in Table 1). Using **30**-*endo*, the preparation of the ester **38**-*endo* was carried out as before (Scheme 11).

Compound **30**-*exo* still remained unavailable. The situation was not improving as alkene **28** eluded all attempts of ionic hydrogenation[38a,38b] (H^+/Et_3SiH) or hydrometallation/protodemetallation (Schwartz's reagent[39] or BH_3·THF[40]). Hydrosilylation/protodesilylation[41] proved not stereoselective (**30**-*endo*/*exo* = 6:4). As a palliative measure, we purified **37**-*exo* from a diastereo-enriched mixture of acids (**37**-*endo*/*exo* = 4:6 produced from **30**, Table 1, Entry 3). Although the chromatographic separation was difficult, we secured enough material to proceed to **38**-*exo*.[42]

With the esters **26** and **38** in hand, the synthesis of the targets **1** was straightforward (cf. Scheme 12). Except in the case of **38**-*exo*, where a substantial amount of uncyclized amide was formed along with **1b-2**-*exo*, possibly due to the steric shielding of the ester by the *exo*-methyl group at C-1.



Scheme 12. Synthesis of the target compounds **1**.

In any case, condensation of ethylenediamine (EDA) on the esters **26** or **38**, according to the method of Neef,[43] produced compounds **1** and completed our chemistry foray.

Conclusions

In summary, we have described the synthesis of rigid analogues of the α_2-antagonist possessing a benzo-fused bicyclo[3.2.0]heptane skeleton. The carbocyclic framework of **2** was efficiently assembled using an intramolecular [2+2] cycloaddition. From this point onwards the chemistry provided surprises at every turn. Among the most significant were: 1) the different outcomes in the reduction of **2** depending on the metal hydride used as the reducing agent; 2) the thermal elimination of the TCI derivatives of alcohols **12**-*endo* and **12**-*exo* leading to either a ring transformation or clean *syn* elimination depending upon the stereochemistry of the alcohol precursor; 3) the complete *exo* selectivity seen with the ionic hydrogenation of **21** and the hydrogenation of the intracyclic π-bond in **34**. A practical route to *exo*-1-methyl derivatives remains to be defined and work in this direction is in progress. The preparation of target compounds of the type **1**, as reported herein, could be extended to structural analogues whenever warranted by pharmacological results.

Experimental Section

General: Melting points were determined using a Büchi 530 melting point apparatus and are not corrected. ^1H NMR spectra were recorded using a Bruker Avance 400 spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C. Chemical shifts are reported in ppm (δ) relative to an internal standard of tetramethylsilane. IR spectra were obtained using a Nicolet FT 510 P spectrophotometer. Microanalyses were obtained using a Fison EA 1108/CHN analyzer. Mass spectra (TSQ, 7000 Finnigan, Thermoelectron Corporation) were obtained by electron spray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI) techniques.

Analytical thin-layer chromatography was carried out on precoated plates (silica gel, 60 F 254, Merck).

Diethyl 2-(2-Isopropenylbenzyl)malonate (5b): To a suspension of sodium hydride (7.28 g, 182 mmol, 60% in mineral oil) and anhydrous dimethoxyethane (DME) (150 mL), diethyl malonate was added dropwise (27.6 mL, 182 mmol) while the temperature was maintained below 30 °C. After stirring at room temperature for 2 h, a solution of 2-isopropenylbenzyl chloride (28.80 g, 173 mmol) in DME (20 mL) was added dropwise at 5 °C (ice bath). The mixture was stirred at room temperature overnight then poured into iced water. The product was extracted twice with EtOAc, washed with water and brine. The organic layer was dried ($MgSO_4$), filtered and the solvent was distilled in vacuo. The crude oil was purified by vacuum distillation to give **5b** as a colorless oil (23.30 g, 58%); b.p. 125–130 °C (6×10^{-5} atm). R_f = 0.31 [cyclohexane/EtOAc (9:1)]. IR (film): $\tilde{\nu}$ = 1750, 1735 (C=O), 1640 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.18 (t, 6 H, CH_2CH_3), 2.07 (s, 3 H, CH_3), 3.27 (d, J = 8.0 Hz, 2 H, CH_2), 3.71 (t, J = 8.0 Hz, 1 H, CH), 4.41 (m, 4 H, CH_2O), 4.89 (s, 1 H, CH=), 5.23 (s, 1 H, CH=), 7.10 (m, 1 H, H arom.), 7.16 (m, 3 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.9, 24.9, 32.0, 52.8, 61.3, 115.5, 126.6, 126.8, 128.3, 129.6, 134.1, 144.0, 145.0, 169.0 ppm. MS (APCI): m/z = 291.2 $[M + H]^+$.

Ethyl 2-(2-Isopropenylbenzyl)malonate, Sodium Salt (6b): To a solution of **5b** (23.97 g, 82 mmol) in anhydrous EtOH (200 mL) at room temperature, NaOH (2 N in EtOH, 41.25 mL, 82.5 mmol) was added dropwise. The solution was stirred at room temperature overnight. The precipitate of disodium salt was filtered off (1.82 g, 8%), and the filtrate was concentrated in vacuo. The monosodium salt was crystallized by addition of diethyl ether (500 mL), filtered, washed with diethyl ether and dried in vacuo at 50 °C to give **6b** (16.40 g, 69.9%) as a white solid; decomp. at 245–250 °C. 284.29; R_f = 0.48 [toluene/dioxane/AcOH (70:20:5)]. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 1.14 (t, 3 H, CH_2CH_3), 2.08 (s, 3 H, CH_3), 3.22 (m, 2 H, CH_2), 3.65 (dd, J = 6.8, 9.2 Hz, 1 H, CH), 4.08 (q, 2 H, CH_2O), 4.90 (s, 1H CH=), 5.30 (s, 1 H, CH=), 7.20–7.26 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 16.0, 27.0, 35.4, 59.3, 64.8, 118.0, 129.5, 130.1, 131.2, 132.4, 138.2, 146.9, 148.3, 176.4, 178.8 ppm.

Ethyl 2a-Methyl-1-oxo-1,2,2a,7-tetrahydrocyclobuta[*a*]indene-7a-carboxylate (2b): To a suspension of **6b** (16.40 g, 58 mmol) in anhydrous xylene (150 mL), a solution of acetyl chloride (4.3 mL, 60 mmol) in xylene (10 mL) was added dropwise whilst stirring and cooling in an ice bath. The mixture was stirred at room temperature overnight, then diluted with xylene (100 mL) and heated at reflux for 3 h in a Dean-stark apparatus containing molecular sieves (4 Å) and K_2CO_3. The suspension was cooled, filtered and the xylene was evaporated in vacuo. The crude product was purified by vacuum distillation to give **2b** (10.73 g, 76%) as a pale yellow oil; b.p. 105–110 °C (10^{-4} atm). R_f = 0.28 [cyclohexane/EtOAc (9:1)]. IR (film): $\tilde{\nu}$ = 1789, 1731 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.33 (t, 3 H, CH_2CH_3), 1.69 (s, 3 H, CH_3), 3.12 (d, J = 17.2 Hz, 1 H, 2-H), 3.40 (d, J = 16.8 Hz, 1 H, 7-H), 3.59 (d, J = 17.2 Hz, 1 H, 2-H), 3.60 (d, J = 16.8 Hz, 1 H, 7-H), 4.28 (m, 2 H, CH_2O), 7.24 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3, 21.4, 36.5, 49.9, 61.5, 61.8, 79.8, 123.6, 125.0, 127.9, 128.0, 140.6, 146.5, 169.1, 204.3 ppm. MS (APCI): m/z = 245.0 $[M + H]^+$.

7a-(Hydroxymethyl)-2a-methyl-2,2a,7,7a-tetrahydro-1*H*-cyclobuta-[*a*]inden-1-ol (Mixture of 12-*endo*/*exo*): To a solution of $LiAlH_4$ (1 M in THF, 70 mL, 70 mmol) diluted with anhydrous THF (65 mL), whilst stirring at –10 °C, a solution of **2b** (7.73 g, 31.6 mmol) in THF (30 mL) was added dropwise and the resulting solution was stirred at room temperature overnight. Whilst stirring in an ice bath, water (2.7 mL), NaOH (30%, 2 mL) and water (19 mL) were added successively. After stirring at room temperature for 1 h, the solid was filtered off and the filtrate was concentrated in vacuo. The residue was extracted twice with EtOAc, washed with water and brine. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated to give a crude mixture of isomers **12-*endo*/*exo*** (68:32) as determined by ^1H NMR spectroscopy. Separation of the diastereoisomers by silica gel chromatography, eluting with CH_2Cl_2/MeOH (97:3), gave **12-*exo*** (0.88 g, 13.5%) as a white solid; m.p. 88–90 °C. R_f = 0.21 [cyclohexane/EtOAc (1:1)]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.35 (s, 3 H, CH_3), 2.16 (dd, J = 8.0, 11.2 Hz, 1 H, 2-H), 2.50 (dd, J = 7.6, 11.2 Hz, 1 H, 2-H), 2.87 (d, J = 16.4 Hz, 1 H, 7-H), 2.89 (s, exchangeable with D_2O, 1 H, OH), 2.99 (d, J = 16.4 Hz, 1 H, 7-H), 3.29 (d, J = 6.0 Hz, exchangeable with D_2O, 1 H, OH), 3.94 (dd, simplified to d with D_2O, J = 11.2 Hz, 1 H, CH_2O), 4.08 (m, simplified to t with D_2O, J = 7.6 Hz, 1 H, 1-H), 4.21 (dd, simplified to d with D_2O, J = 11.2 Hz, 1 H, CH_2O), 7.18, (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.6, 40.8, 45.2, 45.9, 56.6, 63.7, 72.2, 123.5, 125.3, 126.9, 127.0, 141.2, 151.4 ppm. $C_{13}H_{16}O_2$ (204.26): calcd. C 76.44, H 7.90; found C 76.38, H 7.95. MS (ESI+): m/z = 227.1 $[M + Na]^+$. Compound **12-*endo***: White solid (4.00 g, 61.9%); m.p. 118–120 °C. R_f = 0.13 [cyclohexane/EtOAc (1:1)]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.40 (s, 3 H, CH_3), 1.60 (br. s, exchangeable with D_2O, 1 H, OH), 1.86 (dd, J = 8.4, 12.4 Hz, 1 H, 2-H), 1.92 (br. s, exchangeable with D_2O, 1 H, OH), 2.48 (dd, J = 8.4, 12.4 Hz, 1 H, 2-H), 2.93 (d, J = 17.2 Hz, 1 H, 7-H), 3.52 (d, J = 17.2 Hz, 1 H, 7-H), 3.74 (d, J = 10.8 Hz, 1 H, CH_2O), 3.82 (d, J = 10.8 Hz, 1 H, CH_2O), 4.37 (t, J = 7.4 Hz, 1 H, 1-H), 7.09 (m, 1 H, H arom.), 7.17 (m, 2 H, H arom.), 7.27 (m, 1 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 19.2, 34.3, 43.9, 46.1, 56.9, 66.2, 67.3, 121.7, 124.9, 126.5, 126.6, 143.4, 151.2 ppm. $C_{13}H_{16}O_2$ (204.26): calcd. C 76.44, H 7.90; found C 76.19, H 7.97. MS (ESI+): m/z = 227.1 $[M + Na]^+$.

7a-(*tert*-Butylcarbonyloxymethyl)-2a-methyl-2,2a,7,7a-tetrahydro-1*H*-cyclobuta[*a*]inden-*endo*-1-ol (13-*endo*): To a solution of **12-*endo*** (9.44 g, 46.2 mmol) in anhydrous CH_2Cl_2 (150 mL) and triethylamine (TEA) (7.7 mL, 55.3 mmol), 4-(dimethylamino)pyridine (0.10 g, 0.8 mmol) was added. To the cooled reaction mixture (ice bath) a solution of pivaloyl chloride (6.0 mL, 48.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the mixture was stirred at room temperature overnight. The suspension was poured into HCl (0.5 N), extracted twice with EtOAc and washed with water and brine. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The crude product was purified by silica gel chromatography eluting with cyclohexane/EtOAc (8:2) to give **13-*endo*** (6.67 g, 50%) as a pale yellow oil. R_f = 0.35 [cyclohexane/EtOAc (7:3)]. IR (film): $\tilde{\nu}$ = 3440 (OH), 1728 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.14 [s, 9 H, $C(CH_3)_3$], 1.39 (s, 3 H, CH_3), 1.68 (br. s, exchangeable with D_2O, 1 H, OH), 1.89 (dd, J = 6.2, 12.4 Hz, 1 H, 2-H), 2.50 (dd, J = 8.3, 12.4 Hz, 1 H, 2-H); 2.83 (d, J = 17.2 Hz, 1 H, 7-H), 3.52 (d, J = 17.2 Hz, 1 H, 7-H), 4.13 (d, J = 11.6 Hz, 1 H, CH_2O), 4.25 (d, J = 11.6 Hz, 1 H, CH_2O), 4.33 (m, 1 H, 1-H), 7.09 (m, 1 H, H arom.), 7.16 (m, 2 H, H arom.), 7.24 (m, 1 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 19.6, 27.1, 34.2, 38.8, 44.4, 46.7, 55.7, 66.9, 67.1, 121.8, 124.6, 126.7, 143.1, 151.1, 178.8 ppm. MS (ESI+): m/z = 311.2 $[M + Na]^+$. Reduction of the ketone **21** by KBH_4 in MeOH at room temperature overnight gave a mixture of isomers **13-*endo*/*exo*** (86:14), determined by ^1H NMR spectroscopy. Purification by

silica gel chromatography eluting with cyclohexane/EtOAc (85:15) gave 70% of **13**-*endo*.

7a-(*tert*-Butylcarbonyloxymethyl)-2a-methyl-2,2a,7,7a-tetrahydro-1*H*-cyclobuta[*a*]indene-*exo*-1-ol (13-*exo*): Prepared from **12**-*exo* as described above for **13**-*endo* (51%) as a white solid; m.p. 78–80 °C. R_f = 0.38 [cyclohexane/EtOAc (7:3)]. IR (KBr): $\tilde{\nu}$ = 3450 (OH), 1701 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 [s, 9 H, $C(CH_3)_3$], 1.34 (s, 3 H, CH_3), 2.17 (dd, J = 7.6, 11.2 Hz, 1 H, 2-H), 2.20 (d, J = 6.0 Hz, exchangeable with D_2O, 1 H, OH), 2.53 (dd, J = 7.6, 11.2 Hz, 1 H, 2-H), 2.94 (d, J = 16.4 Hz, 1 H, 7-H), 3.04 (d, J = 16.4 Hz, 1 H, 7-H), 4.04 (q, simplified to t with D_2O, J = 7.6 Hz, 1 H, 1-H), 4.37 (d, J = 11.6 Hz, 1 H, CH_2O), 4.59 (d, J = 11.6 Hz, 1 H, CH_2O), 7.15–7.22 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.0, 27.2, 38.8, 40.0, 44.8, 46.4, 55.5, 64.1, 71.4, 123.4, 125.2, 127.0, 127.1, 141.0, 150.8, 178.5 ppm. $C_{18}H_{24}O_3$ (288.37): calcd. C 74.97, H 8.39; found C 75.02, H 8.45. MS (ESI+): m/z = 289.2 $[M + H]^+$. Stereoselective reduction of the ketone **21** with silane: To a solution of **21** (1.72 g, 6 mmol) in anhydrous CH_2Cl_2 (7 mL) NH_4F (0.58 g, 15.6 mmol) and Et_3SiH (2.5 mL, 15.6 mmol) were added. Whilst stirring in an ice bath, CF_3CO_2H (4.6 mL, 60 mmol) was added dropwise and the mixture was stirred at room temperature for 4 h. The mixture was poured into ice/water and neutralized with $NaHCO_3$. The organic layer was washed with water, dried, filtered and the solvent evaporated in vacuo. The crude mixture containing **13**-*exo* and the corresponding trifluoroacetate **48**[22b] was dissolved in EtOAc (15 mL) and stirred overnight with K_2CO_3 (1.38 g, 10 mmol) in water (15 mL). The organic layer was decanted, washed with water, dried ($MgSO_4$) and filtered. The residue, which comprised only the *exo* isomer (^1H NMR determination), was purified by silica gel chromatography eluting with cyclohexane/EtOAc (9:1) to give **13**-*exo* (1.25 g, 72%).

7a-(*tert*-Butylcarbonyloxymethyl)-2a-methyl-1,2,2a,7-tetrahydrocyclobuta[*a*]inden-1-one (21): To a mixture of **13**-*endo* and **13**-*exo* (4.42 g, 15 mmol) (originating from the pivaloylation of diols **12**-*endo*/*exo*) in anhydrous CH_2Cl_2 (70 mL), molecular sieves (4 Å) (7.70 g), *N*-methylmorpholine *N*-oxide (2.70 g, 23 mmol) and tetrapropylammonium perruthenate (0.15 g, 0.42 mmol) were added successively. The mixture was stirred at room temperature for 4 h, then filtered and the solvent was evaporated in vacuo. The residue was purified by silica gel chromatography eluting with cyclohexane/EtOAc (95:5) to give **21** (3.25 g, 74%) as a white solid; m.p. 66–68 °C. R_f = 0.54 [cyclohexane/EtOAc (7:3)]. IR (KBr): $\tilde{\nu}$ = 1780, 1735 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.21 [s, 9 H, $C(CH_3)_3$], 1.69 (s, 3 H, CH_3), 2.88 (d, J = 16.8 Hz, 1 H, 2-H), 3.04 (d, J = 17.2 Hz, 1 H, 7-H), 3.33 (d, J = 16.8 Hz, 1 H, 2-H), 3.34 (d, J = 17.2 Hz, 1 H, 7-H), 4.30 (d, J = 12.0 Hz, 1 H, CH_2O), 4.44 (d, J = 12.0 Hz, 1 H, CH_2O), 7.16–7.29 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.1, 27.1, 36.9, 38.7, 46.6, 61.5, 62.4, 73.2, 123.7, 124.9, 127.6, 127.9, 140.1, 148.7, 177.9, 211.1 ppm. $C_{18}H_{22}O_3$ (286.36): calcd. C 75.49, H 7.74; found C 75.20, H 7.80. MS (ESI+): m/z = 287.2 $[M + H]^+$.

7a-(*tert*-Butylcarbonyloxymethyl)-1-*exo*-[(1*H*-imidazol-1-ylcarbonothioyl)oxy]-2a-methyl-2,2a,7,7a-tetrahydro-1*H*-cyclobuta[*a*]indene (15-*exo*): A suspension of **13**-*exo* (3.95 g, 13.7 mmol), thiocarbonyldiimidazole (4.84 g, 27.0 mmol) and anhydrous THF (80 mL) was refluxed for 4.5 h. The solvent was evaporated in vacuo and the oily residue extracted four times with diethyl ether. The diethyl ether was evaporated and the residue purified by silica gel chromatography eluting with cyclohexane/EtOAc (85:15) to give **15**-*exo* (4.27 g, 78%) as a pale yellow solid; m.p. 124–126 °C. R_f = 0.24 [cyclohexane/EtOAc (7:3)]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.11 [s, 9 H, $C(CH_3)_3$], 1.42 (s, 3 H, CH_3), 2.49 (dd, J = 8.0, 12.0 Hz, 1 H, 2-H), 2.75 (dd, J = 8.0, 12.0 Hz, 1 H, 2-H), 3.12 (d, J = 16.6 Hz, 1 H, 7-H), 3.39 (d, J = 16.6 Hz, 1 H, 7-H), 4.51 (s, 2 H, CH_2O), 5.54 (t, J = 7.8 Hz, 1 H, 1-H), 7.03 (s, 1 H, H imidazole), 7.21–7.28 (m, 4 H, H arom.), 7.57 (s, 1 H, H imidazole), 8.31 (s, 1 H, H imidazole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.1, 27.0, 38.8, 40.2, 41.4, 47.2, 56.0, 63.2, 79.8, 117.7, 123.6, 125.4, 127.5, 127.6, 131.0, 137.0, 140.7, 149.2, 178.5, 183.2 ppm. MS (ESI+): m/z = 399.2 $[M + H]^+$.

7a-(*tert*-Butylcarbonyloxymethyl)-2a-methyl-2a,7-dihydrocyclobuta[*a*]indene (19): Neat **15**-*exo* (4.27 g, 10.7 mmol) was heated at 240–245 °C for 1.5 h. The mixture was cooled to room temperature and then dissolved in diethyl ether. The suspension was filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography eluting with cyclohexane/EtOAc (9:1) to afford **19** (2.70 g, 93%) as a colorless oil. R_f = 0.55 [cyclohexane/EtOAc (7:3)]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.19 [s, 9 H, $C(CH_3)_3$], 1.49 (s, 3 H, CH_3), 2.93 (d, J = 17.6 Hz, 1 H, 7-H), 2.97 (d, J = 17.6 Hz, 1 H, 7-H), 4.27 (d, J = 11.4 Hz, 1 H, CH_2O), 4.31 (d, J = 11.4 Hz, 1 H, CH_2O), 6.01 (d, J = 2.6 Hz, 1 H, CH=), 6.35 (d, J = 2.6 Hz, 1 H, CH=), 7.18 (s, 4 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.9, 27.2, 35.3, 38.8, 57.4, 61.6, 61.7, 122.7, 126.1, 126.3, 127.0, 136.3, 141.6, 147.3, 147.7, 178.5 ppm. To a mixture of **27** (4.39 g, 10.5 mmol), diisopropylethylamine (7.02 mL, 42.5 mmol), $Pd(OAc)_2$ (0.23 g, 1.05 mmol) and triphenylphosphane (0.55 g, 2.1 mmol) in DMF (58 mL), formic acid (1.58 mL, 42.0 mmol) was added. The solution was stirred at 60 °C for 1 h. Then EtOAc was added and the organic layer was washed with brine, dried, filtered and concentrated. The residue was purified by silica gel chromatography to give **19** (2.58 g, 91%). The spectroscopic data are identical to those above.

7a-(*tert*-Butylcarbonyloxymethyl)-2a-methyl-2,2a,7,7a-tetrahydro-1*H*-cyclobuta[*a*]indene (23): The alkene **19** (2.75 g, 10.2 mmol) was hydrogenated in the presence of Pd/C (10%, 0.25 g) in EtOH (50 mL) under a low pressure of hydrogen (balloon). After 4 h, the catalyst was filtered off and the filtrate concentrated in vacuo to give **23** (2.70 g, 98%) as a colorless oil. R_f = 0.60 [cyclohexane/EtOAc (9:1)]. IR (film): $\tilde{\nu}$ = 1730 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.21 [s, 9 H, $C(CH_3)_3$], 1.30 (s, 3 H, CH_3), 1.76 (m, 1 H, 1-H), 1.89 (m, 2 H, 2-H), 2.18 (m, 1 H, 1-H), 2.79 (d, J = 16.4 Hz, 1 H, 7-H), 3.04 (d, J = 16.4 Hz, 1 H, 7-H), 4.26 (d, J = 11.2 Hz, 1 H, CH_2O), 4.30 (d, J = 11.2 Hz, 1 H, CH_2O), 7.18–7.23 (m, 4 H, H arom.) ppm. MS (ESI+): m/z = 273.2 $[M + H]^+$.

(2a-Methyl-2,2a,7,7a-tetrahydrocyclobuta[*a*]inden-7a-yl)methanol (24): A solution of **23** (2.65 g, 9.73 mmol) in EtOH (90%, 25 mL) and NaOH (10 N, 6 mL) was refluxed for 5 h. EtOH was distilled off and water added. The mixture was extracted twice with EtOAc, washed with brine and dried. The residue was purified by silica gel chromatography eluting with cyclohexane/EtOAc (7:3) to give **24** (1.30 g, 71%) as a pale yellow oil. R_f = 0.33 [cyclohexane/EtOAc (7:3)]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.31 (s, 3 H, CH_3), 1.35 (t, J = 5.2 Hz, exchangeable with D_2O, 1 H, OH), 1.74 (m, 1 H, 1-H), 1.92 (m, 2 H, 2-H), 2.13 (m, 1 H, 1-H), 2.81 (d, J = 16.0 Hz, 1 H, 7-H), 3.09 (d, J = 16.0 Hz, 1 H, 7-H), 3.87 (d, J = 4.8 Hz, simplified to s with D_2O, 2 H, CH_2O), 7.16–7.26 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.6, 25.7, 33.4, 41.8, 51.1, 51.8, 66.1, 123.3, 125.2, 126.7, 126.9, 142.0, 151.7 ppm.

2a-Methyl-1,2,2a,7-tetrahydrocyclobuta[*a*]indene-7a-carboxylic Acid (25): A stock solution of H_5IO_6/CrO_3 was prepared by dissolving H_5IO_6 (11.40 g, 50 mmol) and CrO_3 (0.02 g, 1 mol-%) in wet acetonitrile (114 mL, H_2O content 0.75%, v/v). This stock solution

(13.7 mL, 6 mmol) was added to a solution of **27** (0.45 g, 2.4 mmol) in wet acetonitrile (8 mL) and cooled in an ice bath. The mixture was stirred at 0–5 °C for 3 h then quenched by addition of a solution of Na_2HPO_4 (1.20 g, 8.5 mmol) in water (20 mL). The mixture was extracted twice with EtOAc, washed with water and brine. The organic layers were dried ($MgSO_4$), filtered and the crude carboxylic acid was purified by silica gel chromatography eluting with CH_2Cl_2/CH_3OH (95:5) to give **25** (0.39 g, 79%) as a white solid; m.p. 102–104 °C. R_f = 0.46 [cyclohexane/EtOAc (1:1)]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.40 (s, 3 H, CH_3), 1.80 (m, 1 H, 2-H), 2.03 (m, 1 H, 1-H), 2.39 (m, 1 H, 2-H), 2.63 (m, 1 H, 1-H), 2.97 (d, J = 16.6 Hz, 1 H, 7-H), 3.70 (d, J = 16.6 Hz, 1 H, 7-H), 7.19 (m, 1 H, H arom.), 7.26 (m, 3 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.9, 25.3, 34.1, 41.7, 56.0, 56.7, 123.1, 125.1, 127.2, 127.3, 141.6, 149.5, 181.2 ppm. $C_{13}H_{14}O_2$ (202.24): calcd. C 77.20, H 6.98; found C 76.92, H 6.95. MS (ESI–): m/z = 201.1 $[M - H]^-$.

Methyl 2a-Methyl-1,2,2a,7-tetrahydrocyclobuta[*a*]indene-7a-carboxylate (26): To asolution of carboxylic acid **25** (0.83 g, 4.1 mmol), K_2CO_3 (0.69 g, 5.0 mmol) and tetramethylethylenediamine (0.2 mL, 1.3 mmol), iodomethane (1 mL, 16.0 mmol) was added dropwise. After stirring at room temperature overnight, the mixture was poured into ice/water and extracted twice with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with cyclohexane/EtOAc (95:5) to give **26** (0.74 g, 83%) as a pale yellow oil. R_f = 0.50 [cyclohexane/EtOAc (9:1)]. IR (film): $\tilde{\nu}$ = 1725 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.29 (s, 3 H, CH_3), 1.78 (m, 1 H, 2-H), 1.99 (m, 1 H, 1-H), 2.33 (m, 1 H, 2-H), 2.61 (m, 1 H, 1-H), 2.94 (d, J = 16.6 Hz, 1 H, 7-H), 3.69 (d, J = 16.6 Hz, 1 H, 7-H), 3.77 (s, 3 H, OCH_3), 7.16 (m, 1 H, H arom.), 7.25 (m, 3 H, H arom.) ppm.

2-(2a-Methyl-1,2,2a,7-tetrahydrocyclobuta[*a*]inden-7a-yl)-4,5-dihydro-1*H*-imidazole (1b-1): To trimethylaluminum (2 M solution in toluene, 1.62 mL, 3.24 mmol), diluted with anhydrous toluene (10 mL) maintained at –10 °C, ethylenediamine (0.23 mL, 3.44 mmol) was added dropwise. After stirring at room temperature for 0.5 h, a solution of the ester **26** (0.47 g, 1.64 mmol) in toluene (2 mL) was added dropwise and the mixture refluxed for 2 h. Whilst cooling (ice bath), water (1.5 mL) was slowly added and stirring was continued at room temperature for 0.5 h. The organic layer was decanted, diluted with EtOAc, washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by chromatography on neutral alumina eluting with CH_2Cl_2/CH_3OH (95:5) to give **1b-1** (0.27 g, 72.5%) as an amorphous solid. R_f = 0.30 [$CH_2Cl_2/CH_3OH/NH_4OH$ (80:18:2)]. The hydrochloride salt was crystallized from EtOH/EtOAc to give a white solid; m.p. 245–250 °C (sublimation); chemical purity by HPLC: 98.4%. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 1.37 (s, 3 H, CH_3), 2.01–2.13 (m, 2 H, 1-H, 2-H), 2.32 (m, 1 H, 1-H), 2.46 (m, 1 H, 2-H), 3.28 (d, J = 17.0 Hz, 1 H, 7-H), 3.45 (d, J = 17.0 Hz, 1 H, 7-H), 4.01 (m, 4 H, H imidazoline), 7.38 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 24.2, 28.0, 35.9, 45.3, 47.1, 52.9, 61.0, 126.1, 128.2, 130.7, 130.8, 143.3, 151.5, 176.3 ppm. $C_{15}H_{19}ClN_2$ (262.78): calcd. C 68.56, H 7.29, N 10.66; found C 68.69, H 7.36, N 10.67. MS (ESI+): m/z = 227.2 $[M + H]^+$.

7a-(*tert*-Butylcarbonyloxymethyl)-2a-methyl-1-methylene-1,2,2a,7-tetrahydrocyclobuta[*a*]indene (28): To a solution of NaH (60% in mineral oil, 1.12 g, 28 mmol), anhydrous THF (55 mL) and DMSO (10 mL) at room temperature, methyltriphenylphosphonium bromide (7.50 g, 21 mmol) was added portionwise. The suspension obtained was stirred at room temperature for 2 h. A solution of **21** (4.00 g, 14 mmol) in THF (15 mL) was added dropwise and the suspension was stirred at room temperature overnight. The mixture was poured into iced water and extracted twice with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The triphenylphosphane oxide by-product was precipitated from diisopropyl ether, filtered off and the filtrate was concentrated. The residue was purified by silica gel chromatography eluting with cyclohexane/EtOAc (95:5) to give **28** (3.36 g, 84%) as a colorless oil. R_f = 0.49 [cyclohexane/EtOAc (95:5)]. IR (film): $\tilde{\nu}$ = 1730 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.20 [s, 9 H, $C(CH_3)_3$], 1.44 (s, 3 H, CH_3), 2.65 (dt, J = 1.7, 15.4 Hz, 1 H, 2-H), 2.90 (dt, J = 2.7, 15.4 Hz, 1 H, 2-H), 3.05 (d, J = 16.0 Hz, 1 H, 7-H), 3.10 (d, J = 16.0 Hz, 1 H, 7-H), 4.25 (d, J = 11.4 Hz, 1 H, CH_2O), 4.37 (d, J = 11.4 Hz, 1 H, CH_2O), 4.84 (t, J = 2.7 Hz, 1 H, CH=), 5.03 (t, J = 2.7 Hz, 1 H, CH=), 7.18–7.23 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.8, 27.2, 38.8, 40.8, 45.0, 50.4, 57.8, 65.5, 108.3, 123.4, 124.9, 126.9, 127.0, 141.7, 150.4, 150.8, 178.6 ppm. Treatment of ketone **21** with CH_3MgI in diethyl ether at room temperature, followed by dehydration with $POCl_3$ in pyridine gave **28** (38%). The spectroscopic data are identical to those above.

(2a-Methyl-1-methylene-1,2,2a,7-tetrahydrocyclobuta[*a*]inden-7a-yl)methanol (32): To a solution of **28** (1.20 g, 4.2 mmol) in MeOH (6 mL), 3 M KOH in MeOH (9 mL, 27 mmol) was added and the solution refluxed for 8 h. The MeOH was distilled off and water was added. The product was extracted twice with EtOAc, washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with cyclohexane/EtOAc (8:2) to give **32** (0.63 g, 89%) as a pale yellow oil. R_f = 0.39 [cyclohexane/EtOAc (7:3)]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.47 (s, 3 H, CH_3), 1.57 (br. s, exchangeable with D_2O, 1 H, OH), 2.65 (d, J = 15.6 Hz, 1 H, 2-H), 2.87 (d, J = 15.6 Hz, 1 H, 2-H), 3.04 (d, J = 16.8 Hz, 1 H, 7-H), 3.08 (d, J = 16.8 Hz, 1 H, 7-H), 3.87 (br. s, 2 H, CH_2O), 4.90 (s, 1 H, CH=), 5.05 (s, 1 H, CH=), 7.15–7.23 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.4, 40.8, 45.3, 50.1, 60.2, 64.5, 108.0, 123.4, 124.9, 126.8, 126.9, 141.9, 150.6, 152.1 ppm.

7a-(*tert*-Butylcarbonyloxymethyl)-2a-methyl-1-(trifluoromethanesulfonyloxy)-2a,7-dihydrocyclobuta[*a*]indene (27): A solution of **21** (1.00 g, 3.49 mmol) in THF (10 mL) was added dropwise to LiHMDS (1 M in hexane, 4.19 mL, 4.19 mmol) and cooled to –35 °C. A solution of *N*-phenyltriflimide (1.50 g, 4.19 mmol) THF (10 mL) was then added and the solution stirred at room temperature for 1 h. The reaction mixture was diluted with Et_2O, washed with brine, dried ($MgSO_4$), filtered and the solvent was distilled off in vacuo. The residue was purified by silica gel chromatography eluting with cyclohexane/EtOAc (95:5) to give **27** (0.95 g, 65%) as a colorless oil. R_f = 0.57 [cyclohexane/EtOAc (9:1)]. IR (film): $\tilde{\nu}$ = 1733 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.21 [s, 9 H, $C(CH_3)_3$], 1.56 (s, 3 H, CH_3), 2.88 (d, J = 17.6 Hz, 1 H, 7-H), 3.22 (d, J = 17.6 Hz, 1 H, 7-H), 4.35 (d, J = 12.0 Hz, 1 H, CH_2O), 4.38 (d, J = 12.0 Hz, 1 H, CH_2O), 5.77 (s, 1 H, 2-H), 7.22 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.9, 27.0, 32.7, 38.8, 55.6, 61.6, 64.6, 118.4 (q, J = 321.1 Hz, CF_3), 123.1, 125.9, 126.3, 126.9, 127.9, 140.4, 141.5, 144.8, 178.2 ppm. MS (ESI+): m/z = 436.1 $[M + NH_4]^+$.

7a-(*tert*-Butylcarbonyloxymethyl)-1,2a-dimethyl-2a,7-dihydrocyclobuta[*a*]indene (34): To a solution of **27** (0.80 g, 1.91 mmol) in THF (8 mL) at 0 °C, $Pd(PPh_3)_4$ (0.08 g) was added. The mixture was stirred for 15 min, then Me_2Zn (1.2 M in toluene, 4.78 mL,

5.74 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 h, then quenched at 0 °C with water. The precipitate was filtered off and the filtrate was extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent was distilled in vacuo. The residue was purified by silica gel chromatography eluting with cyclohexane/EtOAc (97:3) to give **34** (0.49 g, 90%) as a colorless oil. R_f = 0.23 [cyclohexane/EtOAc (95:5)]. IR (film): $\tilde{\nu}$ = 1729 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.20 [s, 9 H, $C(CH_3)_3$], 1.44 (s, 3 H, 2a-CH_3), 1.65 (s, 3 H, 1-CH_3), 2.83 (d, J = 17.2 Hz, 1 H, 7-H), 2.97 (d, J = 17.2 Hz, 1 H, 7-H), 4.28 (d, J = 11.6 Hz, 1 H, CH_2O), 4.33 (d, J = 11.6 Hz, 1 H, CH_2O), 6.01 (s, 1 H, 2-H), 7.16 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.5, 17.1, 27.2, 33.4, 38.9, 57.4, 58.5, 66.9, 122.7, 126.2, 126.3, 126.8, 139.5, 141.7, 145.9, 148.5, 178.6 ppm. MS (APCI): m/z = 285.3 $[M + H]^+$.

7a-(*tert*-Butylcarbonyloxymethyl)-1-*endo*,2a-dimethyl-1,2,2a,7-tetrahydrocyclobuta[*a*]indene (30-*endo*): Compound **34** (1.22 g, 0.77 mmol) in anhydrous EtOH (2 mL) was hydrogenated in the presence of PtO_2 (0.02 g) under a low pressure of hydrogen (balloon). After 1.5 h, the catalyst was filtered off and the filtrate concentrated in vacuo to give **30** (0.20 g, 92%) (*endo*/*exo* > 95:5 as determined by ^1H NMR spectroscopy) as a colorless oil. R_f = 0.35 [cyclohexane/EtOAc (95:5)]. IR (film): $\tilde{\nu}$ = 1729 (C=O) cm^{-1}. ^{1}NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.91 (d, J = 6.8 Hz, 3 H, C^1–CH_3), 1.16 [s, 9 H, $C(CH_3)_3$], 1.36 (s, 3 H, 2a-CH_3), 1.58 (m, 1 H, 2-H), 2.31 (m, 1 H, 2-H, 1-H), 2.89 (d, J = 17.2 Hz, 1 H, 7-H), 3.15 (d, J = 17.2 Hz, 1 H, 7-H), 4.17 (d, J = 11.2 Hz, 1 H, CH_2O), 4.23 (d, J = 11.2 Hz, 1 H, CH_2O), 7.14 (m, 4 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 15.1, 16.4, 20.8, 27.1, 30.1, 36.0, 38.8, 41.2, 49.7, 50.8, 68.5, 122.3, 124.2, 126.5, 126.7, 143.0, 152.1, 178.7 ppm. MS (APCI): m/z = 287.3 $[M + H]^+$.

2-(1-*endo*,2a-Dimethyl-1,2,2a,7-tetrahydrocyclobuta[*a*]inden-7a-yl)-4,5-dihydro-1*H*-imidazole (1b-2-*endo*): Compound **1b-2**-*endo* was prepared from **38**-*endo* as described for **1b-1**. The crude product was purified by silica gel chromatography eluting with CH_2Cl_2/MeOH/NH_4OH (95:5:0.5) to give **1b-2**-*endo* (68%) as a white solid; m.p. 106–107 °C. R_f = 0.17 [CH_2Cl_2/MeOH/NH_4OH (90:9:1)]. IR (KBr): $\tilde{\nu}$ = 3239 (NH), 1598 (C=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.04 (d, J = 7.1 Hz, 3 H, 1-CH_3), 1.38 (s, 3 H, 2a-CH_3), 1.60 (dd, J = 8.5, 11.3 Hz, 1 H, 2-H), 2.18 (dd, J = 9.6, 11.3 Hz, 1 H, 2-H), 3.20 (d, J = 17.6 Hz, 1 H, 7-H), 3.25 (m, 1 H, 1-H), 3.41 (d, J = 17.6 Hz, 1 H, 7-H), 3.51 (m, 2 H, H imidazoline), 3.60 (m, 2 H, H imidazoline), 7.09 (m, 1 H, H arom.), 7.18 (m, 2 H, H arom.), 7.25 (m, 1 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 15.9, 20.3, 28.5, 36.3, 41.2, 46.9, 52.8, 53.6, 122.2, 124.6, 126.7, 126.9, 143.5, 150.5, 170.6 ppm. $C_{16}H_{20}N_2$ (240.35): calcd. C 79.96, H 8.39, N 11.66; found C 79.85, H 8.35, N 11.27. MS (ESI+): m/z = 241.1 $[M + H]^+$.

2-(1-*endo*,2a-Dimethyl-1,2,2a,7-tetrahydrocyclobuta[*a*]inden-7a-yl)-4,5-dihydro-1*H*-imidazole (1b-2-*exo*): Compound **1b-2**-*exo* was prepared from **38**-*exo* as described for **1b-1**. R_f = 0.20 [CH_2Cl_2/MeOH/NH_4OH (90:9:1)]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.06 (d, J = 6.8 Hz, 3 H, 1-CH_3), 1.43 (s, 3 H, 2a-CH_3), 2.01 (t, J = 10.4 Hz, 1 H, 2-H), 2.19 (t, J = 12.0 Hz, 1 H, 2-H), 2.29 (m, 1 H, 1-H), 2.97 (d, J = 16.0 Hz, 1 H, 7-H), 3.46 (d, J = 16.0 Hz, 1 H, 7-H), 3.65 (br. s, 4 H, H imidazoline), 7.19–7.26 (4 H, H arom.) ppm.^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 15.3, 22.9, 35.6, 41.6, 42.4, 49.6, 51.9, 55.9, 123.6, 125.0, 126.8, 126.9, 140.9, 151.4, 167.8 ppm. MS (ESI+): m/z = 241.1 $[M + H]^+$.

Supporting Information Available (see footnote on the first page of this aricle): Experimental and analytical data for compounds **2a**, **5a**, **8**, **10**, **14**, **15**, **16**, **17**, **18**, **20**, **22**, **29**, **33**, **36**, **37**, **38**, **39**, **40**, **41**, **43**, **44**, **45** and **48**.

Acknowledgments

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gave isomeric cyclobutanones (see also: B. B. Snider, E. Ron, B. W. Burbaum, *J. Org. Chem.* **1987**, *52*, 5413–5419). b) While this work was in progress, Orion Corporation published a patent application in which compounds related to **1** were claimed. In this application, however, it was not clear how the 1,2,2a,7-tetrahydrocyclobut[*a*]indene skeleton had been prepared. Moreover, neither experimental protocols nor characterization data were provided to support structure identification: Orion Corporation, *New Polycyclic Indanylimidazoles with Alpha2 Adrenergic Activity*, WO 85698, **2001**; *Chem. Abstr.* **2001**, *135*, 357928.

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[11] Attempts at generating ketene **3** by dehydrohalogenation (W. T. Brady, Y. F. Giang, *J. Org. Chem.* **1985**, *50*, 5177) or elimination of TsOH (W. T. Brady, A. P. Marchand, Y. F. Giang, A.-H. Wu, *Synthesis* **1987**, 395–396) failed completely. For a review on methods used to generate ketenes, see: T. T. Tidwell, "Preparation of Ketenes" in *Ketenes*, Wiley & Sons, New York, **1995**, chapter 3. See also: M. Murakami, I. Usui, M. Hasegawa, T. Matsuda, *J. Am. Chem. Soc.* **2005**, *127*, 1366–1367.

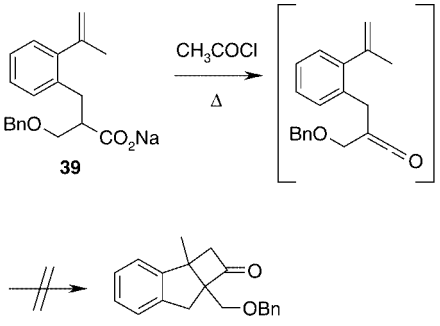
[12] A. D. Allen, M. F. Fenwick, H. Henry-Riyad, T. T. Tidwell, *J. Org. Chem.* **2001**, *66*, 5759–5765.

[13] The reaction of **2b** with $NaBH_4$ was more stereoselective (**8/9** = 95:5, 60% combined yield) than that with $LiBH_4$ (**10/11** = 67:33, 78% combined yield). Reduction of **8** by $LiAlH_4$ gave **10** as the sole product (89% yield). Analytical data for the diester **8** and diol **10** are given in the Supporting Information. The stereochemical relationship between the chains was established by NOE experiments.

[14] Treatment of **2b** with EtONa/EtOH also returned the indane as a mixture of isomers (**8/9** = 6:4).

[15] An example of a bicyclo[3.2.0]heptane-type derivative that ring-opens without activation by a 1,3-dicarbonyl group: C.-S. Hwang, W. Reusch, *Synthesis* **1989**, 428–434.

[16] The most obvious way to avoid having a reactive 1,3-dicarbonyl group in the cycloadduct would be to perform the cycloaddition using precursors such as **39** (see below). Unfortunately, the cycloaddition failed (see Supporting Information for characterization of **39**) which highlighted the importance of ketene activation by the ester function.



[17] Both isomers were separated by chromatography on silica gel (cf. Exp. Sect.).

[18] Reduction of **2b** with DIBAL produced **12**-*endo*/*exo* = 80:20 (60% combined yield). The stereogenic centre at C-1 was destroyed during the synthesis of **1**.

[19] The various methods used are summarized in the Supporting Information.

[20] Although a triphenylmethyl protecting group was introduced with a better regioselectivity than a pivaloyl or a TBDMS group (see Supporting Information), its high molecular weight and sensitivity towards acids or hydrogenolysis were deemed prohibitive.

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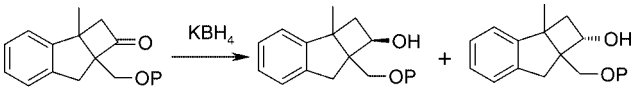
[22] a) The use of metal hydrides as reducing agents gave the *endo*-alcohol preferentially whatever the protecting group "P" on the primary alcohol.



21: P = CO*t*Bu	**13**-*endo* (86%)	**13**-*exo* (14%)
22: P = TBDMS	**14**-*endo* (88%)	**14**-*exo* (12%)
42: P = Tr	**44**-*endo* (85%)	**44**-*exo* (15%)

b) The ionic hydrogenation using Et_3SiH (cf. Scheme 6) gave the opposite facial selectivity to that of metal hydride (for a precedent, see: K. M. Rupprecht, J. Boger, K. Hoogsteen, R. B. Nachbar, J. P. Springer, *J. Org. Chem.* **1991**, *56*, 6180–6188). This reduction initially delivered the *exo*-alcohol as its trifluoroacetate ester **48**, (see Supporting Information for characterization) which was then hydrolysed in situ. Unfortunately, the hydrosilane reduction (Et_3SiH/CF_3CO_2H) did not work for the keto ester **2b**.

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[25] For concomitant reduction of triflates and double bonds, see: D. Comins, Y. Zhang, *J. Am. Chem. Soc.* **1996**, *118*, 12248–12249.

[26] Chromatographic separation proved impractical for the alcohol **33**, the ester **38** and the final imidazoline **1**.

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[30] The reduction in presence of Wilkinson's catalyst required prolonged heating (24 h of refluxing in ethanol). Under these conditions, no isomerization of the double bond to an intracyclic position was detected: R. C. Ronald, M. B. Gewali, B. P. Ronald, *J. Org. Chem.* **1980**, *45*, 2224–2229.

[31] Selectivity of the catalytic hydrogenations was checked at almost every stage en route to **1** (see Supporting Information), but the level of *exo* selectivity never exceeded that obtained for **28** or **29**.

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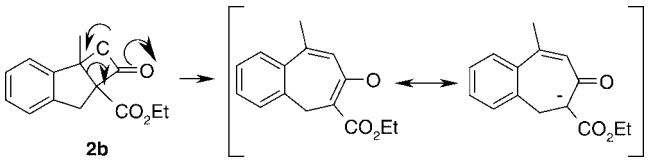
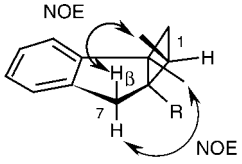
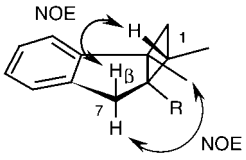
[36] We could not prepare the enol triflate from the keto ester **2b**. We believe that a competing retro-cyclization might be interfering.



[37] The stereochemistry of the methyl group at C-1 in **37** was deduced from NOE experiments. Thus, the positive NOE between 7-H^{β} and either the methyl group or the hydrogen atom at C-1 allowed us to define their orientation. Identification of 7-H^{β} in the ^{1}H NMR spectrum was unambiguously confirmed by NOE (NOE between 7-H^{α} and the methyl group at C-2a).



30-*endo*: R = $CH_2OCOtBu$
37-*endo*: R = CO_2H



37-*exo*: R = CO_2H

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[39] Compound **28** did not react with Schwartz's reagent in THF or toluene, even upon heating: P. Wipf, H. Jahn, *Tetrahedron* **1996**, *52*, 12853–12910; S. Ballenweg, R. Gleiter, W. Krätschmer, *Tetrahedron Lett.* **1993**, *34*, 3737–3740.
[40] Hydroboration of **28** with BH_3·THF (E. A. Hill, P. A. Nylen, J. H. Fellinger, *J. Organomet. Chem.* **1982**, *239*, 279–292) did occur as evidenced by the disappearance of **28** (^{1}H NMR and HPLC). However, upon protonolysis (neat CH_3CO_2H, various temperatures), only traces of the reduced material were formed (<5% by HPLC): H. C. Brown, K. J. Murray, *Tetrahedron* **1986**, *42*, 5497–5504.
[41] F. Lacombe, K. Radkowski, G. Seidel, A. Fürstner, *Tetrahedron* **2004**, *60*, 7315–7324. Hydrosilylation of **28** catalyzed by H_2PtCl_6·H_2O in *i*PrOH/toluene did not work cleanly. In contrast, this reaction could be performed with $Rh_2(OAc)_4$ as the catalyst: B. Marciniec, J. Gulinski, W. Urbaniak, Z. W. Kornetka, *Comprehensive Handbook on Hydrosilylation* (Ed.: B. Marciniec), Pergamon Press, Elmsford, NY, **1992**, pp. 533–544; M. A. Brook, *Silicon in Organic, Organometallic, and Polymer Chemistry*, Wiley & Sons, New York, **2000**, p. 414.
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