Preparation of Conformationally Constrained α_2 Antagonists: The Bicyclo[3.1.0]hexane Approach

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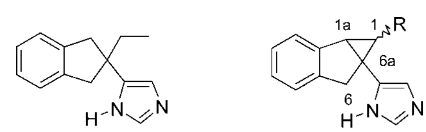
The aim of the research was to discover antagonists at α_2 receptor subtypes potentially more selective than known compounds. We focused on new, conformationally restricted analogues of atipamezole. The key step in the synthetic sequences leading to target compounds relied on a rhodium-catalyzed intramolecular cyclopropanation reaction, the outcome of which varied with the nature of the diazo styrene precursor. Thus, depending on the substitution pattern of the double bond and the electronic properties of the diazo precursors, the cyclopropanes **2** or **7**, naphtalenes **8**, or pyrazolines **17** were formed. The byproducts **8** and **17** originated from different, nonoverlapping mechanisms. Among the racemates synthesized, three compounds (**1a**, **22a**, and **22b**) showed increased selectivity for α_{2A} vs. α_{2B} and α_{2C} receptor subtypes, and consequently were prepared in enantiomerically pure form.

Introduction

Adrenergic receptors mediate many of the peripheral and central actions of adrenaline and noradrenaline. They are extensively but differentially distributed on neurons, effector organs and tissues where they control important homeostatic responses. Adrenergic receptors fall into three major groups: α_1, α_2, and β receptors. The β receptors are subdivided into two main types, β_1 and β_2[1], which, in contrast to α_1 and α_2, frequently coexist in the same tissue. It is remarkable that within the adrenergic receptors class, only α_2-selective antagonists have found no clinical application in humans.[2] We believe, however, that a blockade of α_2 receptors in the appropriate brain regions would have a positive impact on the treatment of a range of neurodegenerative diseases.[3] Although selective, potent, and orally active α_2 antagonists do already exist,[4] none of the α_2 blockers available to us had a sufficient safety margin[5] to advance proof of concept studies in neurodegenerative conditions. So, target validation in humans is yet to be achieved. New hope of improving the separation between neuroprotective and undesirable effects came from the recognition of three α_2 subtypes (i.e., α_{2A}, α_{2B}, and α_{2C})[6] with distinct tissue distributions, and possibly, functions.[7] This, indeed, re-ignited our drug discovery efforts and the search for a compound endowed with α_2-subtype selectivity. Within this framework, we resurfaced atipamezole[8] and set out to explore its conformationally restricted analogues (Figure 1).



atipamezole **1**

Figure 1. Atipamezole and its conformationally restricted analogues of type **1**.

Limiting the conformational freedom of a ligand in order to enhance its selectivity is a classic strategy in medicinal chemistry.[9] Interestingly, atipamezole is selective for α_2 receptors (vs. α_1 and β) but has high and comparable affinities for the different α_2 subtypes. Such a situation seems ideally suited for applying the conformational restriction approach and observing the impact on subtype selectivity, and downstream, on functions. Accordingly, this paper deals with the synthesis of compounds of type **1** (Figure 1), which carry an extra cyclopropane ring relative to atipamezole, and discloses a set of studies directed at the preparation of the benzo-fused polycyclic esters related to **2** (Scheme 1).

As a matter of fact, ring fusion between a bicyclo[3.1.0]-hexane motif and a benzene nucleus freezes the conformation of the polycyclic core in **1**.

Results and Discussion

Synthesis of Cyclopropane Key Intermediates

The synthetic plan for the preparation of compounds of type **1** is shown in Scheme 1.

We intended to synthesize compounds **1**[10] and congeners from esters **2**, which, in turn, would be derived from

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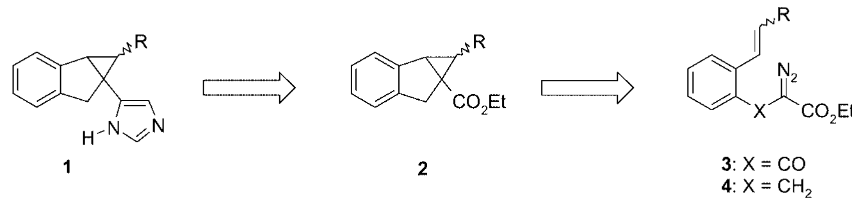
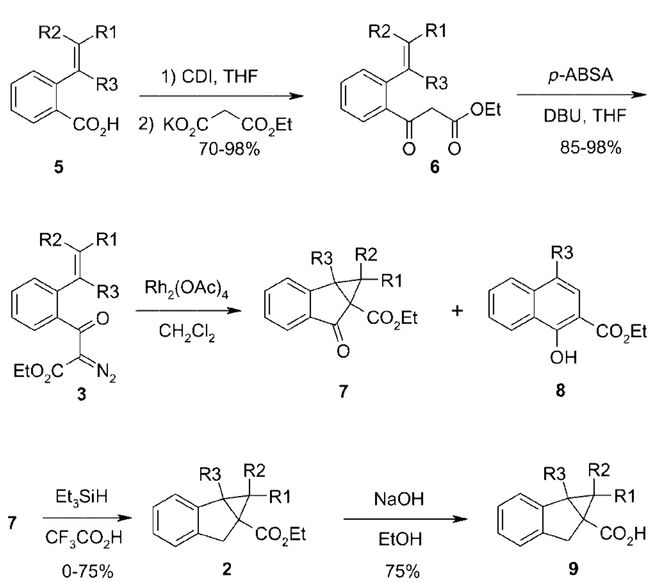


Scheme 1. Retrosynthesis of compounds of type **1**.

the diazo intermediates **3** or **4** (Scheme 1). This approach would offer several advantages: (1) esters **2** could serve to incorporate other functional (or pharmacophoric) groups such as those typically found in the field of α_2 ligands (i.e., 2-imidazoline[4a] or amino[11] groups); and (2) the strategy based on carbenoid chemistry should enable substitution at C-1 with control of the relative stereochemistry; inasmuch as the thermally allowed insertion of a carbene across the π-system of a double bond is a suprafacial (π_{2S}) process.[12] Hence, the geometry of the alkene (*E* or *Z*) in **3** or **4** should define the orientation of the R group (*exo* or *endo*) in **2**.

There are numerous precedents of cyclopropanation making use of an intermolecular reaction between a diazocarbonyl compound and a styrene-type double bond.[13] The intramolecular variant involving aliphatic, diazo-unsaturated substrates has also been extensively employed in organic synthesis.[14] To our surprise, we could find only two examples of limited scope, dating back to 1960, reporting intramolecular cyclopropanations from α-diazoacetophenone precursors resembling **3**.[15] Since then, processes exploiting such a reaction have not been forthcoming. In addition, no precedents on the cyclization of homobenzylic diazo substrates such as **4** have appeared in the literature. So, besides the pharmacological perspective, there is an interest in the synthetic chemistry undertaken.

The initial route to the key intermediates **2** (and **9**) is summarized in Scheme 2.



Scheme 2. Synthesis of the building blocks **2** and **9**.

From the acids **5**,[16] chain extension provided the β-ketoesters **6** in excellent yields.[17] The diazo precursors **3** were then prepared according to the procedure of Davies.[18] Owing to the known thermal sensitivity of diazo derivatives, compounds **3** were purified by filtration through silica gel and then engaged directly in the cyclopropanation step. The results obtained in the Rh^{II}-catalyzed cyclopropanation reactions are summarized in Table 1.

Table 1. Intramolecular cyclopropanation of **3**.[a]

Entry	3	R^1	R^2	R^3	7	Yield, %[b]
1	**a**	H	H	H	**a**	76
2	**b**	CH_3	H	H	**b-*exo***	45
3	**c**	H	CH_3	H	**c-*endo***	44
4	**d**	CH_2CH_3	H	H	**d-*exo***	62
5	**e**	H	CH_2CH_3	H	**e-*endo***	86
6	**f**	H	H	CH_3	**f**	50

[a] All reactions were carried out in CH_2Cl_2 with 3 mol-% of $Rh_2(OAc)_4$ at room temperature. [b] Yields given refer to isolated products.

The cyclopropanation reactions proceeded in fair yields throughout the series (Table 1), notwithstanding (1) the unfavorable entropy change going from **3** to **7**; (2) the build up in strain in the polycyclic system; and (3) the electron-deficient character of the double bond in **3** due to the vinylogous carbonyl function. The reaction also tolerated *E*- and *Z*-alkyl groups on the olefin (entries 2–6). As anticipated at the outset, a high level of stereocontrol at C-1 was achieved in the cyclopropanations.[19]

The isomeric naphthalene byproducts **8**[20] (Scheme 2) were only detected when the styrene double bond was unsubstituted at the terminal position (i.e., **3a** and **3f**), in which cases they approximately accounted for the remaining material balance (vide infra). No product other than **7** and **8** could be characterized in these reactions.

Given that compounds **7** did not rearrange into **8** under the reaction conditions, we tentatively explained the different outcomes by the mechanisms illustrated in Figure 2.

According to the commonly accepted mechanism of Doyle,[21] nucleophilic attack of **3** on the metal catalyst delivered the metal-stabilized carbene **10**. If the mechanism of the cycloaddition is asynchronous, two zwitterionic species could be involved: **11** and/or **12**.

The formation of naphthalene **8** was taken as a piece of evidence in favor of the contribution of a 6-*endo* ring-closure (Figure 2, path *i*), the six-membered ring intermediate **11** then evolving towards **8** possibly by 1,2-hydrogen transfer[22] (path *i-1*). Overall, this mechanism was equivalent to

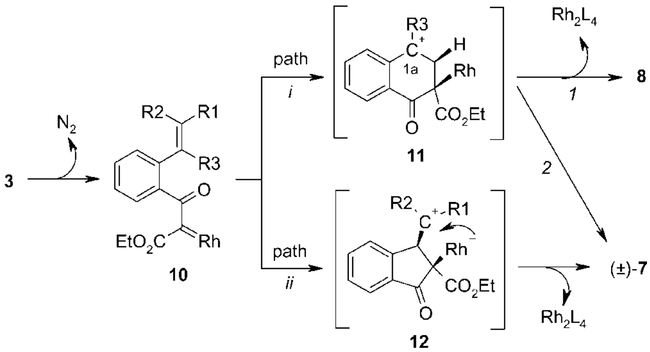


Figure 2. Mechanistic considerations on the formation of compounds **7** and **8**.

a formal insertion of the carbenoid in either one of the vinylic C–H bonds of the styrene terminus. Intermediate **11** might also lead to **7** if the electron-deficient C-1a is intercepted intramolecularly by the rhodium (pathway *i-2*).

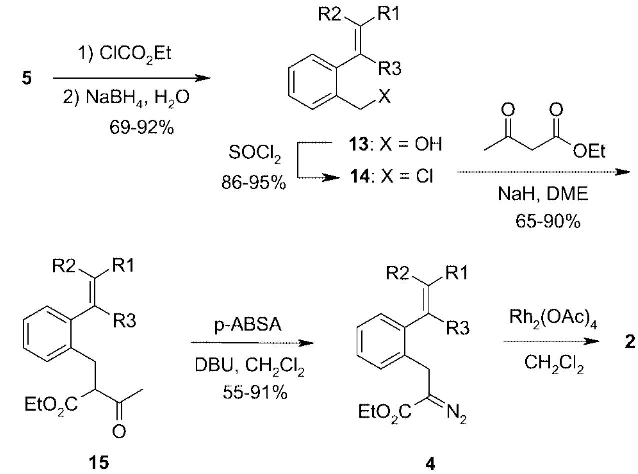
This model would account for the increased proportion of **8f** (approximately 30%) vs. **8a** (approximately 10%) in the cyclopropanation of **3f** and **3a**, respectively, the extra methyl group in **11f** stabilizing the positive charge developing at C-1a, and also rendering elimination thermodynamically more favorable.

A substituent on the olefin terminus (e.g., **3b–e**), irrespective of the double bond stereochemistry, prevented the formation of **8**, thereby ruling out the participation of a 6-*endo* cyclization. It was assumed that, in these cases, the reaction was channeled through **12**, regioselectively (Figure 2, path *ii*).

Reduction of the ketones **7** with triethylsilane in trifluoroacetic acid[23] worked efficiently with **7a** (75%), poorly with **7b** (20%), but failed with **7c–f**.[24] Saponification was generally carried out on crude **2** to facilitate purification, the acids **9** being isolated in pure form by simple acid-base extractions. Thus, the deoxygenation reaction (**7**→**2**) stood as the limiting step when alkyl-substituted cyclopropanes were targeted. From a medicinal chemistry standpoint, however, the carbonyl function at C-6 represented a valuable handle to study substituent effects in this position.[25]

The breakdown experienced in most of the deoxygenations (i.e., **7c–f**) revealed that the derivatives **2c–f** were not attainable by the route above. To overcome this, the cyclopropanation was carried out directly from the deoxo, diazo derivatives **4** instead of **3**.

The revised sequence is outlined in Scheme 3.



Scheme 3. An alternative route to compounds of type **2**.

Thus, reduction of the acids **5**, via their mixed anhydrides, provided the alcohols **13**. Conversion of **13** to the corresponding chlorides **14**, followed by reaction with ethyl acetoacetate produced the β-keto esters **15**. The diazo transfer reaction was then accomplished by the method of Taber.[26] From the β-diazo esters **4**, however, the cyclopropanation promoted by Rh^{II} gave mixed results (Table 2).

Overall, the cyclopropanation from **4** appeared less efficient than from **3** (Table 2). Thus, it worked in moderate yields with *E*- (entries 2,4,7) or disubstituted (entry 8) π-bonds, whereas *Z*- (entries 3,5) or terminal (entry 1) olefins produced only low yields of **2**.

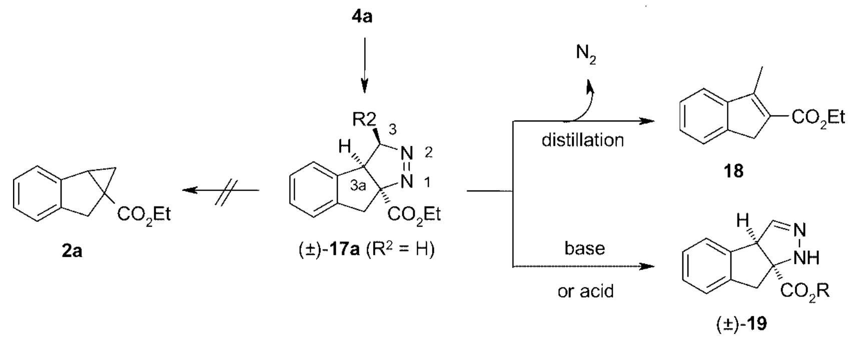
With styrenes **4a**, **4c**, and **4e**, the principal outcome of the reaction was the fused 1-pyrazolines **17** (see Scheme 4).[27] In such substrates, the nucleophilicity of the diazo dipole was sufficient to allow its spontaneous addition across the double bond. As expected, the [3+2] cycloaddition of the diazo dipole proceeded with retention of configuration about the double bond, such that a single stereoisomer of **17** was obtained.[27b,28] In addition, the conversion of **4** into **17** was faster in the presence of the rhodium catalyst; it seemed as if the styrene were activated by coordination with the metal.[29]

In contrast, with substrates **4b**,**d**,**f–h**, the corresponding pyrazolines **17** were not formed, and carbenoid transfer was

Table 2. Intramolecular cyclopropanation of **4**.[a]

Entry	4	R^1	R^2	R^3	2	Yield, %[b]	17	Yield, %[b]
1	**a**	H	H	H	**a**	12	**a**	41
2	**b**	CH_3	H	H	**b**-*exo*	60	**b**	–
3	**c**	H	CH_3	H	**c**-*endo*	18	**c**	38
4	**d**	CH_2CH_3	H	H	**d**-*exo*	43	**d**	–
5	**e**	H	CH_2CH_3	H	**e**-*endo*	3	**e**	24
6	**f**	H	H	CH_3	**f**	32	**f**	–
7	**g**	$(CH_2)_2CH_3$	H	H	**g**-*exo*	42	**g**	–
8	**h**	CH_3	CH_3	H	**h**	65	**h**	–

[a] All reactions were carried out in CH_2Cl_2 with 3 mol-% of $Rh_2(OAc)_4$ at room temperature. [b] Yields given refer to isolated products.



Scheme 4. Attempts of transformations of **17a**.

the major operative pathway (entries 2 and 8), or admittedly, the only one leading to an identifiable product (entries 4, 6, and 7). Clearly, the best substrates to reach compounds of type **2** were those in which the olefin carried a methyl group in the *trans* position (entries 2 and 8).

To capitalize on our effort, we tried to turn **17** into **2** (Scheme 4).

Thermal decomposition of **17a** converted it back to the indene **18**[27a,30] instead of the desired cyclopropane **2a**. No reaction occurred upon photolysis of **17a** at room temperature, despite a successful precedent[31] reported on a closely related structure. Basic or acidic treatment of the 1-pyrazoline **17a** stopped at the stage of the more stable Δ^2 tautomer **19**. Hence, as far as the preparation of **2a** was concerned, **17a** constituted a dead end.

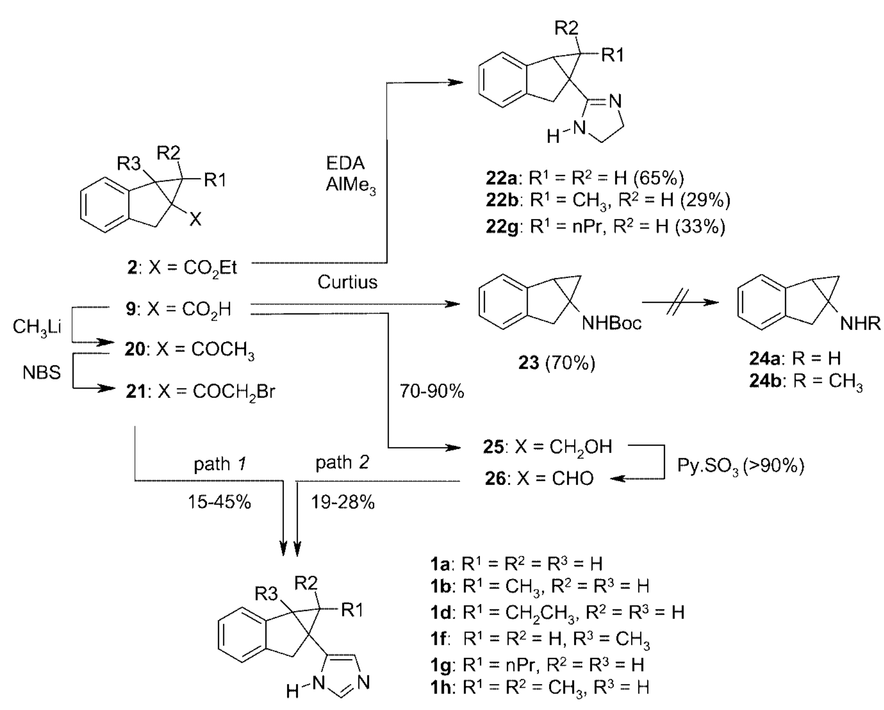
On the bright side, however, both methodologies (cf. Scheme 2 and Scheme 3) were complementary enough to enable us to reach the intended molecules (i.e., **1** and **22**).

Synthesis of Compounds 1 and Congeners

With compounds **2** (and/or **9**) in hand, the synthesis of **1** and congeners (i.e., **22** and **24**) was addressed (Scheme 5).

From the esters **2**, the preparation of the imidazolines **22** was straightforward.[32] The synthesis of the imidazoles **1** was comparatively more demanding and was approached by two different methods. The method of Elz[33] (Scheme 5, pathway *1*) relied on the bromomethyl ketones **21**. The latter were synthesized in two steps from the acids **9**.[34] The method developed by van Leusen[35] (pathway *2*) began with the aldehydes **26** and involved three successive stages: condensation with TosMIC, dehydration, and cyclization of the adduct with ammonia.

Disappointingly, all attempts of synthesis of amines of the type **24** were of no avail. Even though the Curtius rearrangement on the acid **9a**[36] led to the Boc-protected amine **23**, neither removal nor reduction of the BOC group



Scheme 5. Synthesis of the target compounds **1** and congeners.

produced a stable, characterizable product.[37] Except in the case of **24** where a basic nitrogen was linked to the cyclopropane ring, the benzo-fused [3.1.0]hexane system showed a remarkable stability.

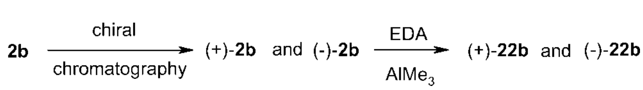
Synthesis of Optically Active Compounds 1 and Congeners

Once the chemistry to **1** and **22** was in place, chirality became the most pressing issue. The success met with chiral rhodium catalysts in asymmetric cyclopropanations[38] prompted us to subject the prochiral compounds **3a** and **4b** to cyclopropanations in the presence of chiral Rh catalysts.[39] All the stereogenic centers present in the target molecules are set in the cyclopropanation step. However, whatever the diazo precursor (**3** or **4**) or the catalyst used, no asymmetric induction was ever observed.[40] Indeed, these negative results discouraged us from investing further effort in this direction.

Next, we wondered whether a chiral auxiliary would perform better in terms of stereoselection. Guided by the work of Taber[41a] and Davies,[41b] we prepared esters of type **3** bearing a motif (+)-menthol or (*R*)-pantolactone. Once again, upon $Rh_2(OAc)_4$ or $Rh_2(S\text{-}DOSP)_4$ promoted reactions (i.e., simple or double stereodifferentiation), no diastereoselectivity was achieved whatsoever.[40]

In the end, we had to use resolution to secure each enantiomer of the pharmacologically most promising racemates for tests (i.e., **1a**, **22a**, and **22b**). The case of **1a** was the most favorable since resolution could be effected on the final material by preparative HPLC on chiral support.[42]

Unlike **1a**, racemates **22a** and **22b** could not be resolved under various separation conditions. Consequently, resolution was carried out on **2b** en route to **22b** (Scheme 6).

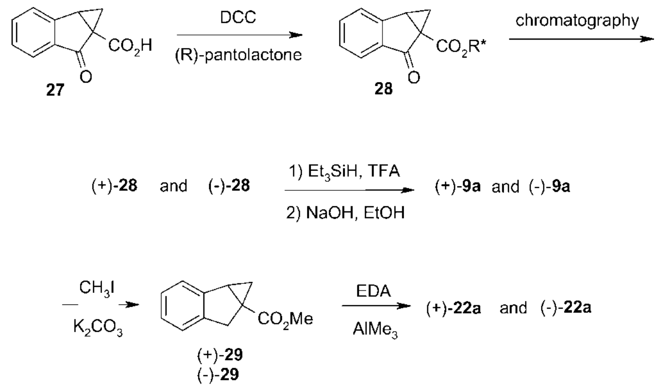


Scheme 6. Resolution of late-stage intermediate **2b**.

Thus, racemate **2b** was resolved by chiral HPLC with excellent optical purity (>99% *ee*) and recovery.[42] From (+)-**2b** and (–)-**2b**, the synthesis of enantiomerically pure substances (+)-**22b** and (–)-**22b** proceeded along the same lines as for the racemic series.

Some chemical modifications were required prior to the resolution of **22a**. Optically pure (*R*)-pentolactone was grafted on **27** (Scheme 7), then the corresponding esters **28** were separated by chromatography on silica gel (>97% *de*). Completion of the synthesis then followed the steps performed on **7a** (cf. Scheme 2).

At this point, until the relationship between biological activity and absolute stereochemistry for ligands **1** and **22** has been clarified, resolution remains more productive than asymmetric synthesis.



Scheme 7. Resolution assisted by a chiral auxiliary.

Conclusion

In summary, we have described the synthesis of novel, conformationally restricted analogues of atipamezole. Two routes to the scarcely represented benzo-fused [3.1.0]hexane core are reported; both rely on an intramolecular insertion of a metallocarbene across the π-system of a styrene double bond. These routes differ, however, in the electronic properties of the diazo substrates involved in the key cyclopropanation step. Importantly, intramolecular cyclopropanation of homobenzylic diazo styrenes (e.g., **4**) to access strained, polycyclic systems has been established. A range of alkyl groups on the cyclopropyl moiety was implemented for SAR studies. The structural variations carried out unraveled, in turn, interesting mechanistic aspects regarding the competition between diazo decomposition/1,3-dipolar cycloaddition and 6-*endo*/5-*exo* ring closure. Pharmacological results showed that **1a**, **22a**, and **22b** exhibited a significant gain in binding selectivity for the α_{2A} over the α_{2B} and α_{2C} receptor subtypes. The improved α_{2A} selectivity observed with compounds **22** warranted further investigations.

Experimental Section

Ethyl *o*-Vinylbenzoylacetate (6a): Step A: a solution of 2-vinyl-benzoic acid[16] (**5a**) (22.00 g, 0.148 mol) and 1,1′-carbonyldiimidazole (23.8 g, 0.147 mol) in anhydrous tetrahydrofuran (135 mL) was stirred at room temperature overnight. Step B: to a suspension of potassium ethyl malonate (50.00 g, 0.294 mol) anhydrous acetonitrile (550 mL), and triethyl amine (61 mL, 0.44 mol) was added portionwise magnesium chloride (35.00 g, 0.367 mol) while maintaining the temperature below 20 °C. The reaction mixture B was stirred at room temperature for 4 h then cooled in an ice bath. The solution A was added dropwise, and the suspension stirred at room temperature overnight. The solvent was removed in vacuo, the residue was taken up in toluene (300 mL), cooled (ice bath), and aqueous HCl (12%, 240 mL) was slowly added. The mixture was warmed to room temperature and extracted twice with ethyl acetate. The combined organic layers were washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **6a** (32.50 g, 98.5%), which was used as such in the next step. A sample was purified by distillation to give a colorless oil: b.p. 134 °C (10^{-4} atm). $C_{13}H_{14}O_3$: 218.24; R_f 0.35 cyclohex/EtOAc (9:1). IR (neat): $\tilde{\nu}$ = 1743, 1689 cm^{-1}. ^1H NMR ($CDCl_3$; mixture of β-keto-ester/enol form, 7:3): δ = 1.23 (t, 3 H), 3.94 (s, 2 H), 4.18 (q, 2 H), 5.37 (d, 1 H, *J* = 10.9 Hz), 5.66 (d, 1 H, *J* = 17.4 Hz), 7.19 (dd, 1 H, *J* = 10.9 Hz, 17.4 Hz), 7.34 (m, 1 H), 7.49 (m, 1 H), 7.60 (m, 2 H) ppm. MS (ESI) 219.0 $[M + H]^+$.

Ethyl (*o*-Vinylbenzoyl)diazoacetate (3a): To a solution of **6a** (29.67 g, 0.136 mol) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (32.60 g, 0.136 mol) in anhydrous THF (300 mL), cooled in an ice bath, was added dropwise a solution of DBU (20.5 mL, 0.136 mol) in THF (25 mL). The mixture was stirred at room temperature overnight, and then concentrated in vacuo (bath $T° <$ 40 °C). The residue was taken up in cyclohex/EtOAc (1:1), the solid formed was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by filtration through a pad of silica gel eluting with CH_2Cl_2 to give **3a** (32.80 g, 98.7%), which was used as such in the next step. A pure sample was obtained by silica-gel chromatography eluting with cyclohex/EtOAc (9:1): $C_{13}H_{12}N_2O_3$: 244.24; R_f 0.39 cyclohex/EtOAc (7:3). IR (neat): $\tilde{\nu}$ = 2144, 1720, 1628 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.15 (t, 3 H), 4.15 (q, 2 H), 5.32 (d, 1 H, *J* = 12 Hz), 5.71 (d, 1 H, *J* = 17.4 Hz), 6.84 (dd, 1 H, *J* = 12 Hz, 17.4 Hz), 7.29 (m, 2 H), 7.40 (t, 1 H), 7.57 (d, 1 H) ppm. MS (ESI) 245.0 $[M + H]^+$.

Ethyl 6-Oxo-1a,6-dihydro-1*H*-cyclopropa[*a*]indene-6a-carboxylate (7a): To a suspension of rhodium(II)acetate dimer (1.93 g, 0.00438 mol) in anhydrous CH_2Cl_2 (250 mL) was added at room temperature a solution of **3a** (35.80 g, 0.146 mol) in CH_2Cl_2 (50 mL). The reaction was slightly exothermic with gas evolution. After stirring at room temperature overnight, the catalyst was filtered off, and the solution was concentrated in vacuo. The residue was purified by silica gel chromatography eluting with cyclohex/EtOAc (9:1) to give **7a** (23.90 g, 75.7%) as a pale orange oil: $C_{13}H_{12}O_3$: 216.23; R_f 0.29 cyclohex/EtOAc (7:3). IR (neat): $\tilde{\nu}$ = 1746, 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.33 (t, 3 H), 1.74 (t, 1 H, *J* = 4.4 Hz), 2.39 (dd, 1 H, *J* = 4 Hz, 7.6 Hz), 3.37 (dd, 1 H, *J* = 4.8 Hz, 7.6 Hz), 4.29 (q, 2 H), 7.35 (t, 1 H), 7.45 (d, 1 H), 7.51 (t, 1 H), 7.70 (d, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.13, 32.04, 38.61, 39.77, 61.56, 124.43, 125.31, 127.63, 134.11, 134.13, 151.46, 168.50, 195.44 ppm. MS (ESI) 216.9 $[M + H]^+$. The byproduct 1-hydroxy-naphthalene-2-carboxylic acid ethyl ester **8a** (14%) was eluted first: R_f 0.55 cyclohex/EtOAc (7:3). The spectroscopic data of **8a** were identical to those previously reported.[20]

Ethyl 1a,6-Dihydro-1*H*-cyclopropa[*a*]indene-6a-carboxylate (2a): To a solution of **7a** (11.80 g, 0.0546 mol) in trifluoroacetic acid (35 mL) cooled in an ice bath, was added dropwise Et_3SiH (21.7 mL, 0.136 mol). The solution was stirred at room temperature overnight, and then poured into cold aqueous $NaHCO_3$ solution and extracted twice with diethyl ether. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography eluting with cyclohex/EtOAc (98:2) gave (6.62 g, 60%) **2a** as a pale yellow oil: b.p. 85 °C (10^{-4} atm). $C_{13}H_{14}O_2$: 202.24; R_f 0.40 cyclohex/EtOAc (9:1). IR (neat): $\tilde{\nu}$ = 1721 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.68 (t, 1 H, *J* = 4.4 Hz), 1.27 (t, 3 H), 1.98 (dd, 1 H, *J* = 4.4 Hz, 8 Hz), 2.95 (m, 1 H), 3.06 (d, 1 H, *J* = 17.2 Hz), 3.72 (d, 1 H, *J* = 17.2 Hz), 4.18 (q, 2 H), 7.14 (m, 3 H), 7.26 (m, 1 H) ppm. MS (APCI) 202.8 $[M + H]^+$.

1a,6-Dihydro-1*H*-cyclopropa[*a*]indene-6a-carboxylic Acid (9a): The crude ester obtained by the reduction of **7a** (5.48 g, 0.025 mol) was saponified with NaOH (10 N, 22 mL) in aqueous EtOH (150 mL, 90%) overnight at room temperature. The solvents were distilled off, and water was added. The mixture was washed twice with Et_2O and acidified with HCl (6 N) while cooling in an ice bath. The precipitate obtained was filtered off, washed with water and dried in vacuo over P_2O_5 to give **9a** (3.32 g, 75%) as a white solid: m.p. 117–119 °C. $C_{11}H_{10}O_2$: 174.19; R_f 0.52 toluene/dioxane/AcOH (75:20:5). ^1H NMR ($CDCl_3$): δ = 0.78 (t, 1 H, *J* = 4.4 Hz), 2.07 (dd, 1 H, *J* = 4 Hz, 8.4 Hz), 3.07 (m, 2 H), 3.71 (d, 1 H, *J* = 17.2 Hz), 7.15 (m, 3 H), 7.28 (m, 1 H) ppm.

Compounds (–) and (+)-9a: Obtained by reduction (Et_3SiH/CF_3CO_2H) and saponification of **(–)-28** and **(+)-28**. The enantiomeric excess was determined by analytical HPLC with a Chiralpack® AD column (Daicel) eluting with hexane/EtOH/TFA (90:10:0.01), 1 mL/min; UV, 220 nm. Compound **(–)-9a** (isolated as a white solid): m.p. 107–109 °C; t_R 8.2 min; 98.4% *ee*. $[\alpha]_D^{25}$ = –207.3 (*c,* 0.53, MeOH). Compound **(+)-9a** (white solid): m.p. 107–109 °C; t_R 6.6 min; 97.1% *ee*. $[\alpha]_D^{25}$ = +206.4 (*c,* 0.404, MeOH).

(1a,6-Dihydro-1*H*-cyclopropa[*a*]inden-6a-yl)-methanol (25a): To a solution of **9a** (11.53 g, 0.066 mol) in anhydrous THF (180 mL), was added *N*-methylmorpholine (7.3 mL, 0.066 mol). To the mixture cooled to –15 °C was added dropwise ethylchloroformate (6.33 mL, 0.066 mol), and the suspension was stirred for 1 h at –15 °C. The precipitate of *N*-methylmorpholine hydrochloride was filtered off, and the filtrate was cooled to –15 °C. To this solution was added dropwise a solution of $NaBH_4$ (5.60 g, 0.146 mol) in water (60 mL). The suspension was stirred overnight at room temperature, and then concentrated in vacuo. Water was added, and the mixture was acidified (1 N HCl). It was then extracted twice with EtOAc. The combined organic layers were washed with aqueous $NaHCO_3$, brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with cyclohex/EtOAc (7:3) to give **25a** (9.80 g, 92%) as a pale yellow oil: $C_{11}H_{12}O$: 160.21; R_f 0.22 cyclohex/EtOAc (7:3). IR (neat): $\tilde{\nu}$ = 3346 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.39 (t, 1 H, *J* = 4 Hz), 1.15 (dd, 1 H, *J* = 4.4 Hz, 8.0 Hz), 1.56 (br. s, 1 H), 2.29 (ddd, 1 H, *J* = 1.2 Hz, 2.8 Hz, 4.4 Hz), 3.05 (d, 1 H, *J* = 16.8 Hz), 3.26 (d, 1 H, *J* = 16.8 Hz), 3.75 (d, 1 H, *J* = 11.4 Hz), 3.8 (d, 1 H, *J* = 11.4 Hz), 7.10 (m, 2 H), 7.14 (m, 1 H), 7.25 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.37, 28.36, 30.81, 37.27, 67.46, 123.17, 125.39, 125.44, 125.96, 142.11, 143.23 ppm.

1a,6-Dihydro-1*H*-cyclopropa[*a*]indene-6a-carboxaldehyde (26a): To a solution of **25a** (2.15 g, 0.0134 mol) in anhydrous DMSO (10 mL) was added triethyl amine (5.6 mL, 0.04 mol). The temperature was maintained below 10 °C while sulfur trioxide pyridine complex (6.39 g, 0.04 mol) was added portionwise. After stirring at room temperature for 4 h, the solution was poured into ice water and extracted twice with EtOAc. The organic layer was washed with 5% aqueous citric acid solution, brine, and dried over $MgSO_4$. The crude **26a** (2.12 g) was used as such in the next step. A pure sample was obtained by silica gel chromatography eluting with cyclohex/EtOAc (9:1): $C_{11}H_{10}O$: 158.19; R_f 0.43 cyclohex/EtOAc (7:3). IR (neat): $\tilde{\nu}$ = 1699 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.04 (t, 1 H, *J* = 4.8 Hz), 2.00 (dd, 1 H, *J* = 4.8 Hz, 8.4 Hz), 2.96 (d, 1 H, *J* = 17.6 Hz), 3.07 (m, 1 H), 3.73 (d, 1 H, *J* = 17.6 Hz), 7.13–7.30 (m, 4 H), 9.14 (s, 1 H) ppm.

2-(1a,6-Dihydro-1*H*-cyclopropa[*a*]inden-6a-yl)-4,5-dihydro-1*H*-imidazole (22a): To trimethylaluminum (1.5 mL, 0.003 mol, 2 M in toluene) and anhydrous toluene (10 mL), cooled to –10 °C, was added dropwise ethylenediamine (0.23 mL, 0.00345 mol). After stirring for 0.5 h at room temperature, a solution of **2a** (0.47 g, 0.0023 mol) in toluene (2 mL) was added dropwise, and the mixture was refluxed for 2 h. The reaction mixture was cooled (ice bath), then water (1.3 mL) was slowly added, and stirring was maintained for 0.5 h at room temperature. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by neutral alumina chromatography eluting with CH_2Cl_2/MeOH (98:2) to give **22a** (0.31 g, 67%): R_f 0.30 CH_2Cl_2/MeOH/NH_4OH (90:9:1). The product was crystallized as the oxalate salt from EtOH/EtOAc to yield a white solid (0.28 g 62%): m.p. 164–166 °C; chemical purity (HPLC): 98.5%. ^{1}H NMR ([D$_6$]DMSO): δ = 0.93 (t, 1 H, J = 4.8 Hz), 2.03 (dd, 1 H, J = 4.8 Hz, 8.4 Hz), 3.24 (d, 1 H, J = 16 Hz), 3.29 (dd, 1 H, J = 4.8 Hz, 8.4 Hz), 3.54 (d, 1 H, J = 16 Hz), 3.83 (s, 4 H), 7,18 (m, 2 H), 7.25 (m, 1 H), 7.36 (m, 1 H) ppm; $C_{15}H_{16}N_2O_4$ (288.29): calcd. C 62.49, H 5.59, N 9.72; found C 62.46, H 5.72, N 9.66. MS (APCI) 199.1 [M + H]$^+$.

Compounds (+) and (–)-22a: Prepared from **(+)-29** and **(–)-29** as described for **22a**. Enantiomeric purity was determined by HPLC with a Chiralcel® OD column (Daicel) eluting with hexane/EtOH/diethylamine (95:5:0.02), 1 mL/min; UV, 220 nm. Compound **(+)-22a** hydrochloride: crystallized from EtOH/Et_2O, white solid, m.p. 245–250 °C (sublimation). $[\alpha]_D^{25}$ = +218.2 (c, 0.37, MeOH); t_R 17.5 min; 96.7% *ee.* ^{13}C NMR ([D$_6$]DMSO): δ = 24.84, 26.43, 35.74, 36.38, 44.01, 123.17, 125.38, 126.38, 126.60, 139.59, 142.76, 171.82 ppm. $C_{13}H_{15}ClN_2$ (234.73): calcd. C 66.52, H 6.44, N 11.93; found C 66.34, H 6.65, N 11.71. Compound **(–)-22a** hydrochloride: crystallized from EtOH/Et_2O, white solid: m.p. 245–250 °C (sublimation). $[\alpha]_D^{25}$ = –219.9 (c, 0.47, MeOH); t_R 19.3 min; 97.5% *ee.* ^{13}C NMR ([D$_6$]DMSO): δ = 24.83, 26.41, 35.74, 36.37, 44.02, 123.17, 125.38, 126.39, 126.60, 139.59, 142.75, 171.83 ppm. $C_{13}H_{15}ClN_2$ (234.73): calcd. C 66.52, H 6.44, N 11.93; found C 66.25, H 6.45, N 11.69.

2-(1-*exo*-Methyl-1a,6-dihydro-1*H*-cyclopropa[*a*]inden-6a-yl)-4,5-dihydro-1*H*-imidazole (22b): The product was crystallized as the fumaric acid salt from EtOH/EtOAc to give a white solid: m.p. 133–135 °C; R_f 0.18 CH_2Cl_2/MeOH/NH_4OH (80:18:2); chemical purity (HPLC): 97.3%. ^{1}H NMR ([D$_6$]DMSO): δ = 1.08 (m, 1 H), 1.17 (d, 3 H), 3.15 (d, 1 H, J = 3.6 Hz), 3.29 (d, 1 H, J = 17.2 Hz), 3.35 (d, 1 H, J = 17.2 Hz), 3.82 (s, 4 H), 6.43 (s, 2 H), 7.13 (m, 2 H), 7.19 (m, 1 H), 7.32 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 12.13, 29.89, 32.66, 37.56, 37.75, 44.78, 123.06, 125.21, 126.14, 126.22, 140.01, 143.33, 167.76, 169.23 ppm. $C_{18}H_{20}N_2O_4$ (328.36): calcd. C 65.84, H 6.14, N 8.53; found C 65.51, H 6.35, N 8.65. MS (ESI) 213.0 [M + H]$^+$.

Compounds (+) and (–)-22b: Prepared from **(+)-2b** and **(–)-2b** as described for **22a**. Enantiomeric excess was determined with an analytical HPLC Chiralcel® OD column (Daicel) eluting with hexane/EtOH/diethylamine (95:5:0.05), 1 mL/min; UV, 220 nm. Compound **(+)-22b:** fumaric acid salt; crystallized from EtOH/EtOAc; white solid: m.p. 82–84 °C. $[\alpha]_D^{25}$ = +33.3 (*c,* 0.29, MeOH); t_R 14.2 min; 99% *ee.* $C_{18}H_{20}N_2O_4$ (328.36): calcd. C 65.84, H 6.14, N 8.53; found C 65.71, H 5.99, N 8.28. Compound **(–)-22b:** oxalic acid salt; crystallized from EtOH; white solid: m.p. 139–141 °C. $[\alpha]_D^{25}$ = –45.2 (*c,* 1.27, MeOH); t_R 12.3 min; 98.8% *ee.* $C_{16}H_{18}N_2O_4$ (302.32): calcd. C 63.56, H 6.00, N 9.27; found C 63.86, H 6.17, N 9.49.

(*E*)-2-(1-Propenyl)-benzenemethanol (13b): To a suspension of (*E*) 2-(2-propenyl)benzoic acid[16] **5b** in anhydrous THF (550 mL) was added N-methyl morpholine (23.1 mL, 0.21 mol). To the reaction mixture maintained at –10 °C was added dropwise ethyl chloroformate (20.1 mL, 0.21 mol). The suspension was stirred at –10 °C for 2 h, and the precipitate of *N*-methylmorpholine hydrochloride was filtered off. To the filtrate cooled to –10 °C was added dropwise a solution of $NaBH_4$ (17.50 g, 0.462 mol) in water (176 mL). The mixture was stirred for 2.5 h at –15 °C, and then at room temperature overnight. The solvent was removed in vacuo, HCl (1 N) was added, and the mixture was extracted twice with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ solution (10%), and brine, then dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to give **13b** (25.91 g, 80.6%) as a pale yellow oil which was used without purification in the next step. A pure sample was obtained by silica gel chromatography eluting with cyclohex/EtOAc (7:3). $C_{10}H_{12}O$: 148.20; R_f 0.55 cyclohex/EtOAc (1:1). ^{1}H NMR ($CDCl_3$): δ = 1.65 (br. s, 1 H), 1.92 (d, 3 H, J = 6.6 Hz), 4.73 (s, 2 H), 6.17 (dq, 1 H, J = 6.6 Hz, 15.6 Hz), 6.70 (d, 1 H, J = 15.6 Hz), 7.19–7.27 (m, 2 H), 7.32 (d, 1 H), 7.44 (d, 1 H) ppm.

(*E*)-2-(1-Propenyl)-benzyl Chloride (14b): To **13b** (25.89 g, 0.175 mol) in anhydrous $CHCl_3$ (150 mL) maintained at –10 °C, was added dropwise thionyl chloride (13.5 mL, 0.193 mol). After stirring for 0.5 h at –10 °C and for 3 h at room temperature, the reaction mixture was washed with water, aqueous $NaHCO_3$, and then brine. The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed in vacuo to give **14b** (27.64 g, 94.7%), which was used as such in the next step. $C_{10}H_{11}Cl$: 166.65; R_f 0.73 cyclohex/EtOAc (7:3).

(*E*)-2-[2-(1-Propenyl)-benzyl]-3-oxobutanoic Acid Ethyl Ester (15b): To a suspension of sodium hydride (60% in mineral oil, 13.20 g, 0.33 mol) in anhydrous DME (180 mL) cooled to 0 °C under nitrogen, was added dropwise ethyl acetoacetate (42 mL, 0.328 mol). After stirring for 0.5 h at 0 °C and for 1.5 h at room temperature, nBu_4NI (6.10 g, 0.0164 mol) was added, followed by a solution of **14b** (27.64 g, 0.166 mol) in DME (40 mL). The reaction mixture was heated at 90 °C for 4 h, then cooled to room temperature, diluted with aqueous HCl (1 N), and extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with cyclohex/EtOAc (1:1) to give **15b** (36.04 g, 84.4%) as a pale orange oil: $C_{16}H_{20}O_3$: 260.32; R_f 0.19 cyclohex/EtOAc (1:1). IR (neat): $\tilde{\nu}$ = 1717, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, 3 H), 1.91 (dd, 3 H, J = 1.2 Hz, 6.6 Hz), 2.15 (s, 3 H), 3.23 (m, 2 H), 3.75 (t, 1 H, J = 7.6 Hz), 4.12 (m, 2 H), 6.12 (dq, 1 H, J = 6.6 Hz, 15.5 Hz), 6.59 (dd, 1 H, J = 1.2 Hz, 15.5 Hz), 7.08–7.18 (m, 3 H), 7.38 (d, 1 H) ppm.

Ethyl 1-*exo*-Methyl-1a,6-dihydro-1*H*-cyclopropa[*a*]indene-6a-carboxylate (2b): To a suspension of rhodium(II)acetate dimer (0.20 g, 0.00045 mol) in anhydrous CH_2Cl_2 (80 mL) was added dropwise, at room temperature, a solution of **4b** (3.63 g, 0.0148 mol, prepared from **15b** as described for **3a**) in CH_2Cl_2 (10 mL). After stirring at room temperature overnight, the catalyst was filtered off, and the solution was concentrated in vacuo. The residue was purified by silica gel chromatography eluting with cyclohex/CH_2Cl_2 (6:4) to give **2b** (1.84 g, 57%) as a pale yellow oil: $C_{14}H_{16}O_2$: 216.27; R_f 0.63 cyclohex/EtOAc (7:3). IR (neat): $\tilde{\nu}$ = 1718 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.03 (m, 1 H), 1.29 (t, 3 H), 1.35 (d, 3 H, J = 6.4 Hz), 2.77 (d, 1 H, J = 4.4 Hz), 3.14 (d, 1 H, J = 17.2 Hz), 3.58 (d, 1H J = 17.2 Hz), 4.22 (m, 2 H), 7.10 (m, 3 H), 7.25 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.92, 14.38, 35.04, 36.00, 37.50, 40.96, 60.47, 123.02, 125.30, 125.94, 126.03, 141.28, 144.51, 172.61 ppm. MS (APCI) 216.9 [M + H]$^+$.

Compounds (+) and (–)-2b: The separation was made by preparative HPLC with a Chiralpack® AD column (Daicel) eluting with hexane/EtOH (99:1), 100 mL/min; UV, 220 nm. Enantiomeric excess was determined with an analytical Chiralpack® AD column eluting with hexane/EtOH (99:1), 1 mL/min; UV, 230 nm. Compound **(+)-2b** was isolated as a pale yellow oil: $[\alpha]_D^{25}$ = +60.6 (*c,* 0.33, MeOH); t_R 6.8 min; 99.6% *ee.* Compound **(–)-2b** (pale yellow oil): $[\alpha]_D^{25}$ = –59.0 (*c,* 0.3, MeOH); t_R 8.1 min; 99.1% *ee.*

1a,6-Dihydro-1*H*-cyclopropa[*a*]indene-6a-methyl Ketone (20a): To a solution of **9a** (5.53 g, 0.0317 mol) and anhydrous Et_2O (80 mL) maintained at –15 °C, was added dropwise MeLi (60 mL, 0.096 mol, 1.6 M in Et_2O). The suspension was stirred at –15 °C for 4 h and at 0 °C for 3 h. Saturated aqueous NH_4Cl solution (50 mL) was added, and the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with cyclohex/CH_2Cl_2 (1:1) to give **20a** (3.55 g, 64%) as a pale yellow oil: $C_{12}H_{12}O$: 172.22; R_f 0.3 cyclohex/EtOAc (9:1). IR (neat): $\tilde{\nu}$ = 1686 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.8 (t, 1 H, *J* = 4.4 Hz), 2.03 (dd, 1 H, *J* = 4.4 Hz, 8.4 Hz), 2.14 (s, 3 H), 3.01 (m, 1 H), 3.05 (d, 1 H, *J* = 17.2 Hz), 3.76 (d, 1 H, *J* = 17.2 Hz), 7.13–7.29 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.83, 26.91, 35.01, 36.82, 39.69, 123.13, 125.59, 126.18, 126.35, 141.05, 143.58, 206.61 ppm. MS (APCI) 173.1 [M + H]$^+$.

1a,6-Dihydro-1*H*-cyclopropa[*a*]indene-6a-α-bromomethyl Ketone (21a): To a solution of diisopropylamine (0.84 mL, 0.006 mol) and anhydrous THF (10 mL) cooled in an ice bath, was added dropwise *n*BuLi (2.4 mL, 0.006 mol, 2.5 M in THF). After 10 min, the solution was cooled to –70 °C. Then **20a** (0.87 g, 0.005 mol) in THF (2 mL) was added, and stirring was maintained for 1 h. A solution of chlorotrimethylsilane (1.71 mL, 0.0135 mol), triethyl amine (0.45 mL, 0.00325 mol), and THF (8 mL) was added, and the mixture was stirred for 2 h at –70 °C. $NaHCO_3$ (0.30 g, 0.0035 mol) was added, followed by aqueous $NaHCO_3$ (50 mL, 5%). The mixture was diluted with Et_2O, the organic layer was washed with brine, dried ($MgSO_4$), and filtered. The volatiles were removed in vacuo to give a pale yellow oil (1.30 g) which was taken up in anhydrous THF (12 mL) and cooled to –70 °C. To this solution were added successively $NaHCO_3$ (0.50 g, 0.006 mol) and *N*-bromosuccinimide (0.89 g, 0.005 mol). The mixture was stirred at –70 °C for 3.5 h and at room temperature overnight. The suspension was poured into aqueous $NaHCO_3$ and extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and the solvent was evaporated off. The residue was purified by silica gel chromatography eluting with cyclohex/EtOAc (95:5) to give **21a** (0.86 g, 67%) as a pale yellow oil: $C_{12}H_{11}BrO$: 251.13; R_f 0.35 cyclohex/EtOAc (9:1). IR (neat): $\tilde{\nu}$ = 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.91 (t, 1 H, *J* = 4.4 Hz), 2.13 (dd, 1 H, *J* = 4.4 Hz, 8.4 Hz), 3.14 (m, 1 H), 3.23 (d, 1 H, *J* = 17.2 Hz), 3.74 (d, 1 H, *J* = 17.2 Hz), 3.98 (d, 1 H, *J* = 12 Hz), 4.05 (d, 1 H, *J* = 12 Hz), 7.14–7.30 (m, 4 H) ppm.

4-(1a,6-Dihydro-1*H*-cyclopropa[*a*]indene-6a-yl)-1*H*-imidazole (1a): A suspension of **21a** (0.85 g, 0.0034 mol), formamidine acetate (0.52 g, 0.005 mol), and liquid ammonia (15 mL) in anhydrous Et_2O (15 mL) was heated overnight at 60 °C. Water was added to the cooled reaction mixture, which was then washed with EtOAc. The organic layer was extracted twice with HCl (1 N), then the combined aqueous layers were made basic (concentrated NaOH) and extracted with EtOAc. The residue was purified by neutral alumina chromatography eluting with CH_2Cl_2/MeOH (95:5) to give **1a** (0.30 g, 38%) as a yellow oil: R_f 0.31 CH_2Cl_2/MeOH/NH_4OH (90:9:1). The product was crystallized as its fumaric acid salt from EtOH/Et_2O to give a white solid (0.25 g): m.p. 150–152 °C; chemical purity (HPLC): 98.3%. ^1H NMR ([D$_6$]DMSO): δ = 0.5 (t, 1 H, *J* = 4 Hz, 8 Hz), 1.71 (dd, 1 H, *J* = 4 Hz, 8 Hz), 2.53 (m, 1 H), 3.18 (d, 1 H, *J* = 17.2 Hz), 3.49 (d, 1 H, *J* = 17.2 Hz), 6.62 (s, 2 H), 6.99 (s, 1 H), 7.10 (m, 2 H), 7.20 (m, 1 H), 7.28 (m, 1 H), 7.65 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 23.61, 25.65, 32.80, 38.74, 122.85, 125.09, 125.29, 125.79, 133.94, 134.65, 141.29, 146.09, 165.96 ppm. $C_{17}H_{16}N_2O_4$ (312.31): calcd. C 65.37, H 5.16, N 8.97; found C 65.05, H 5.19, N 8.85. MS (APCI) 197.0 [M + H]$^+$.

Compounds (+) and (–)-1a: The separation was made by preparative HPLC with a Chiralpack® AD column (Daicel) eluting with hexane/EtOH (9:1), 100 mL/min; UV, 220 nm. Enantiomeric excess was determined with an analytical HPLC Chiralpack® AD column (Daicel) eluting with cyclohexane/EtOH (9:1), 1 mL/min; UV, 220 nm. Compound **(+)-1a:** fumaric acid salt, crystallized from EtOH/EtOAc, white solid: m.p. 152–154 °C. $[\alpha]_D^{25}$ = +108.5 (*c,* 0.32, MeOH); t_R 7.6 min; 99.8% *ee.* $C_{17}H_{16}N_2O_4$ (312.31): calcd. C 65.37, H 5.16, N 8.97; found C 65.12, H 5.27, N 8.83; chemical purity (HPLC): 99.9%. Compound **(–)-1a:** fumaric acid salt, crystallized from EtOH/EtOAc, white solid: 152.154 °C. $[\alpha]_D^{25}$ = –106.2 (*c,* 0.35, MeOH); t_R 11.2 min; 99% *ee.* $C_{17}H_{16}N_2O_4$ (312.31): calcd. C 65.37, H 5.16, N 8.97; found C 65.10, H 5.32, N, 8.84; chemical purity (HPLC): 99.6%.

4-(1,1-Dimethyl-1a,6-dihydro-1*H*-cyclopropa[*a*]indene-6a-yl)-1*H*-imidazole (1h): To a suspension of *t*BuOK (0.30 g, 0.0026 mol) in anhydrous DME (3 mL), maintained at –40 °C, was added dropwise a solution of tosylmethyl isocyanide (TosMIC) (0.37 g, 0.0019 mol) in DME (3 mL). At –40 °C was then added **26h** (0.35 g, 0.0019 mol) in DME (3 mL). After 1 h at –40 °C, the cold mixture was poured into ice-water, acidified with acetic acid, and then extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and the solvents were evaporated to dryness. The residue was taken up in DME (2 mL), then TEA (1.3 mL, 0.0093 mol) and $POCl_3$ (0.2 mL, 0.002 mol) were added at –15 °C. The mixture was stirred at 0 °C for 1 h, then quenched by addition of ice-water. The mixture was extracted by CH_2Cl_2, washed with brine, dried, filtered, and evaporated under reduced pressure. The residue was treated with a methanolic ammonia solution (7 mL, 4 N) and heated at 45 °C overnight. The volatiles were evaporated off, the residue was taken up in HCl (1 N), and the aqueous layer was washed with EtOAc and made basic (concentrated NaOH), and then extracted with EtOAc. After evaporation of the solvent, the residue was purified by silica gel chromatography eluting with CH_2Cl_2/MeOH (95:5) to give **1h** (0.10 g, 24%) as an orange oil: R_f 0.40 CH_2Cl_2/MeOH (95:5). The product was crystallized as its fumaric acid salt from EtOH/EtOAc to yield a pale yellow solid: mp: 110–112 °C; chemical purity (HPLC): 97.7%. ^1H NMR ([D$_6$] DMSO): δ = 0. 69 (s, 3 H), 0.99 (s, 3 H), 2.61 (s, 1 H), 3.05 (d, 1 H, *J* = 17.6 Hz), 3.18 (s, 1 H, *J* = 17.6 Hz), 6.61 (s, 2 H), 6.83 (s, 1 H), 7.09 (m, 3 H), 7.26 (d, 1 H), 7.58 (d, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 14.82, 23.03, 26.40, 33.64, 38.63, 118.03, 123.58, 123.99, 125.44, 125.90, 134.02, 134.17, 142.61, 143.72, 166.09 ppm. $C_{19}H_{20}N_2O_4$ (340.37): calcd. C 67.04, H 5.92, N 8.23; found C 66.70, H 6.03, N 8.28. MS (ESI) 224.8 [M + H]$^+$.

Supporting Information Available: Experimental and/or analytical data for compounds **1b,d,f,g**, **2c,d,f,g,h**, **6b-f**, **7b-f**, **9b,c,f,h**, **15c-h**, **17a,c,e**, **19**, **20b,d**, **21b,d**, **22g**, **23**, **25f-h**, **26f,h**, **28**, **29**, and esters of type **3** bearing a motif (+)-menthol or (*R*)-pantolactone (see also the footnote on the first page of this article).

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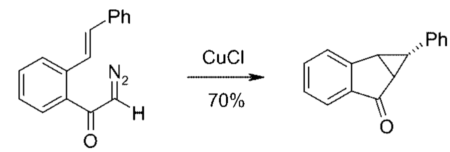

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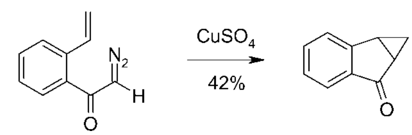

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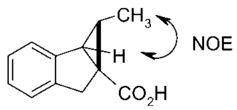
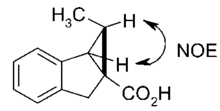
and 1a-H confirming that the methyl at C-1 occupied an *exo* position.



9b



9c

The vicinal coupling constant between 1-H and 1a-H in the ^{1}H NMR spectrum is also indicative of their stereochemical relationship. Thus, $^3J_{syn}$ ($\approx$ 4 Hz) < $^3J_{anti}$ ($\approx$ 10 Hz) according to: L. M. Jackman, S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed., Pergamon Press, Elmsford, N.Y., **1969**, ch. 4-2. For compounds **2b**–**d**, **2g**, and **7b**–**e**, these are collected in the Supporting Information.

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