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Hydroxy-1-aminoindans and Derivatives: Preparation, Stability, and Reactivity

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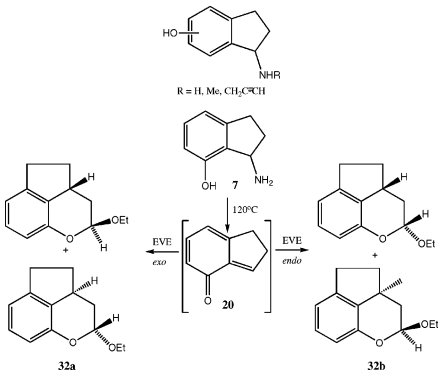

The chemical stability and reactivity of hydroxy-1-aminoindans and their *N*-propargyl derivatives are strongly affected by the position of the OH group and its orientation relative to that of the amino moiety. Thus, the 4- and 6-OH regioisomers were found to be stable, while the 5-OH analogues were found to be inherently unstable as the free bases. The latter, having a para orientation between the OH and the amino moieties, could be isolated only as their hydrochloride salts. 7-Hydroxy-1-aminoindans and 7-hydroxy-1-propargylaminoindans represent an intermediate case; while sufficiently stable even as free bases, they exhibit, under certain experimental conditions, unexpected reactivity. The instability of the 5- and 7-hydroxy-aminoindans is attributed to their facile conversion to the corresponding, reactive quinone methide (QM) intermediates. The *o*-QM obtained from 7-hydroxy-aminoindans was successfully trapped with ethyl vinyl ether via a Diels−Alder reaction to give tricyclic acetals **32a**,**b**.

Introduction

Ladostigil ((*N*-propargyl-1*R*-aminoindan-6-yl)-ethylmethylcarbamate hemi-tartrate) is a novel derivative of the selective irreversible MAO-B inhibitor rasagiline, possessing both cholinesterase- and MAO-inhibitory activity.[1a,b] It is currently under development as an anti-Alzheimer's and neuroprotective drug. (*R*)-6-Hydroxy-*N*-propargyl-1-amimoindan (*R*-6-OHPAI) is a major metabolite of ladostigil, responsible for the MAO-B inhibitory activity of the parent drug (Figure 1).[2] The 4-, 6-, and 7-hydroxy-1-amino-indan (4-, 6-, and 7-OHAI) isomers are synthetically readily accessible,[3] while the 5-OHAI analogue defied our early synthetic attempts. (*R*)-6-Hydroxy-1-aminoindan (***R*-3b**) is a key intermediate in the synthesis of ladostigil. Derivatives of 7-OHAI such as OPC-14117 were reported to be cerebro-protective and central nervous system stimulants.[4a,b] With the exception of **16**, described herein, a literature search has not revealed any other unsubstituted 5-OHAIs. Several 5-hydroxyaminoindan amides are known,[5] and a tricyclic 5-OH−N−Me derivative has been reported.[6] In the framework of our structure activity relationship (SAR) studies on carbam-

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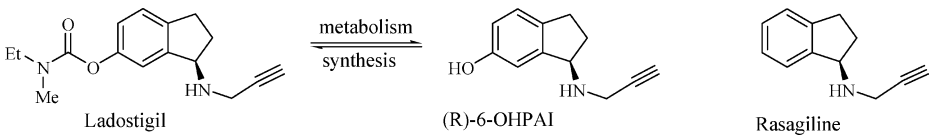
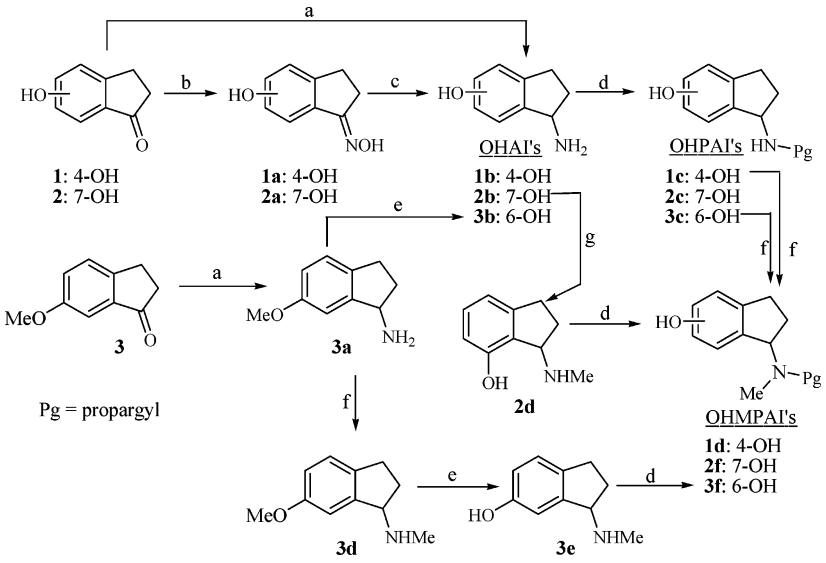


FIGURE 1. Aminoindan derivatives.

SCHEME 1. Synthetic Routes for OHAIs, OHPAIs, and Their *N*-Methyl Analogues[a]



[a] Reaction conditions: (a) $NaCNBH_3$, NH_4OAc; (b) HNH_2OH; (c) H_2; (d) PgBr; (e) HBr; (f) $NaCNBH_3$, $(CH_2O)_n$; (g) (1) HCO_2Et, (2) $LiAlH_4$.

oyl-*N*-propargyl-1-aminoindans, we have investigated the chemistry of the various regioisomers of both OHAIs and their propargyl derivatives OHPAIs.[7] Herein we report on the first synthesis of 5-OHAI and on the stability and reactivity of some OHAIs and OHPAIs. The instability of 5- and 7-OHAIs is attributed to the facile formation of the corresponding quinone methides (QMs). *ortho*-QMs are widely known as reactive and unstable intermediates in organic chemistry. QMs are frequently prepared by pyrolytic or photochemical elimination methods. Different types of *o*-benzyl-substituted systems undergo this kind of elimination under heating or irradiation conditions, most commonly by thermal dehydration of 2-hydroxybenzyl phenols.[8] In the thermal degradation, the temperature range required for the elimination is about 100−600 °C, depending on the structure of the starting material. The addition of metal complexes or various Lewis acids enables the formation of the desired QMs under milder conditions, increasing product stability.[9] Other systems that yield QMs are 2-alkoxymethyl phenols[10] and 2-aminomethyl phenolic Mannich bases, where the amino moiety is tertiary[11] or quaternary[12] **12**. The intermediacy of the QM derived from 7-OHAI **2b** was established by us by a Diels−Alder reaction with ethyl vinyl ether (EVE) to give the tricyclic acetals **32a**,**b**.

Results and Discussion

The preparation of 4-, 6-, and 7-OHAIs and their *N*-methyl and *N*-propargyl derivatives (OHPAIs and OHMPAIs) has been reported.[5] In short, OHAIs were prepared from the corresponding indanones either by conversion of the latter to oximes and subsequent reduction or via a one-step reductive amination ($NaCNBH_3/NH_4OAc$). Propargylation with propargyl bromide (either neat or as an 80% solution in toluene) in acetonitrile or dimethylacetamide afforded the corresponding OHPAIs. *N*-Methyl-OHAIs were obtained either by reductive alkylation

(5) (a) Preparation of *N*-acyltetralinamines and analogues as cholesterol biosynthesis inhibitors. Woitun, E.; Maier, R.; Mueller, P.; Hurnaus, R.; Mark, M.; Eisele, B.; Budzinski, R. M.; Hallermayer, G. Ger. Offen. DE 4438029 A1, 1966. (b) Preparation of *N*-indanylacetamides and related compounds as cholesterol acyltransferase inhibitors. Clader, J. W.; Fevig, T.; Vaccaro, W.; Berger, J. G. Eur. Pat. Appl. EP 508425 A1, 1992. (c) Bicyclic compounds and their use. Oka, Y.; Nishikawa, K.; Miyake, A. Eur. Pat. Appl. EP 51391 A1, 1982. (d) Synthesis and angiotensin converting enzyme inhibitory activity of *N*-benzocycloalkylglycine derivatives. Miyake, A.; Itoh, K.; Inada, Y.; Nishikawa, K.; Oka, Y. *Takeda Kenkyushoho* **1985**, *44* (3/4), 171−185. (e) Chromanyl glycines. Oka, Y.; Nishikawa, K.; Miyake, A. US 4521607 A, 1985.

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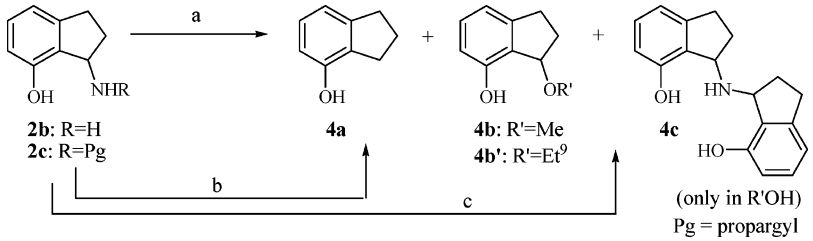
SCHEME 2. Degradation of 7-OHAIs and 7-OHPAIs[a]



[a] Reaction conditions: (a) $NaCNBH_3/(CH_2O)_n$ in MeOH; (b) $NaCNBH_3$, CH_3CN; (c) R'OH (R' = Me/Et).

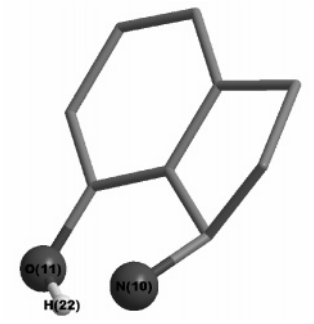
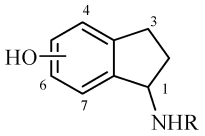


FIGURE 2. Three-dimensional structure of **2b**.

TABLE 1. Proton NMR Shifts of Isomeric Hydroxy-aminoindan Derivatives



	H-C_1		H,H′-C_3	
HO-position	R=H	R=propargyl	R=H	R=propargyl
4-		4.19		2.59,2.77
6-	4.07	4.14	2.52,2.68	2.59,2.74
7-	4.39	4.39	2.68,2.80	2.68,2.85

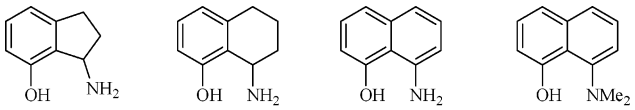


FIGURE 3. Bicyclic analogues of 7-hydroxy-1-aminoindan **2b**.

(NaCNBH$_3$/paraformaldehyde) or by formylation followed by LiAlH$_4$ reduction. *N*-Methyl-OHPAIs (OHMPAIs) were prepared either by propargylating *N*-methyl-OHAIs or by reductive alkylation of OHPAIs (Scheme 1).

7-OHAI and its derivatives have been reported as neuroprotectives[4a,b] and as 5-HT-1A receptor ligands.[13]

We have found 7-OHAI (**2b**), 7-OHPAI (**2c**), and 7-OHMPAI (**2f**) to differ from their 4- and 6-analogues in (i) their polarity, as manifested by TLC, where the former are remarkably less polar than the latter; and (ii) behavior of the amino group, as exhibited during reductive alkylation.

Reductive alkylation of the 7-analogues (successfully applied to the 4- and 6-compounds) did not afford the desired *N*-methylated products. Instead, 4-indanol (**4a**)[14a] and the novel 3-methoxy-4-indanol (**4b**) were isolated in about a 1:4.5 ratio when either **2b** or **2c**[5] was subjected to $NaCNBH_3/(CH_2O)_n$ in MeOH. The refluxing of **2b** in MeOH also led to **4b**, and **4a** was isolated as the sole product upon attempted reductive methylation in acetonitrile (Scheme 2).

To gain some insight into the mechanism(s) leading to the formation of **4a** and **4b**, the acetonitrile was substituted for methanol in the reductive alkylation. In this case, only **4a** was obtained. More intriguing was the observation that mere refluxing of **2b** or **2c** in methanol resulted in a mixture of **4b** and dimer **4c** (Scheme 2). This is in contrast to the 6-analogues, which were found to be stable in this solvent.

In the TLC of the hydroxy-aminoindans, the 7-OH isomer (**2b**) appeared to be the least polar. This behavior of **2b** may be ascribed to appreciable *intramolecular* H-bonding (O−H- -N) present only in this isomer. Molecular modeling (ChemBats3D 2005) showed a distance of 2.15 Å (Figure 2) between the OH proton and the N, which is consistent with the minimum H-bond length (2.5 Å).

The free base OH absorption in DMSO was not always clearly discernible in the ^{1}H NMR spectra of all OHAI regioisomers. Notably, in the spectrum of **2b**, a peak was observed at a nontypical 4.66 ppm, accounting for a $H_2O + NH_2 + OH$ signal. However, the presence of H-bonding in **2b** and **2c** is substantiated by their H−C_1 chemical shifts (Table 1), which are shifted downfield by 0.25 and 0.32 ppm, respectively, relative to the 6-isomers. This is due to the deshielding effect resulting from the lower electron density on C1, which in turn results from a decrease in electron density on the nitrogen due to the H-bonding of its lone pair to the OH proton. The chemical shifts of H,H′−C_3 are apparently not affected by the proximity of the OH group, as evidenced by the practically identical δ values of H,H′−C_3 for the 4- and 6-isomers.

The only report on H-bonding in **2b** is that of Breslow and McClure,[15] who have shown assistance by the phenolic group in the cleavage of an amide in a carboxypeptidase A model. To the best of our knowledge, H-bonding in 8-hydroxy-1-aminotetralin has not been reported. However, this phenomenon has been investigated in 1-amino-8-hydroxy-naphthalenes **6** and **7** (OH and amine in the peri position in the fully aromatic analogues; Figure 3) by Musso,[16] who has shown, using IR spectroscopy, a strong intramolecular interaction between the OH and NH_2 groups. The unusual acidity of *N*,*N*-dimethyl-

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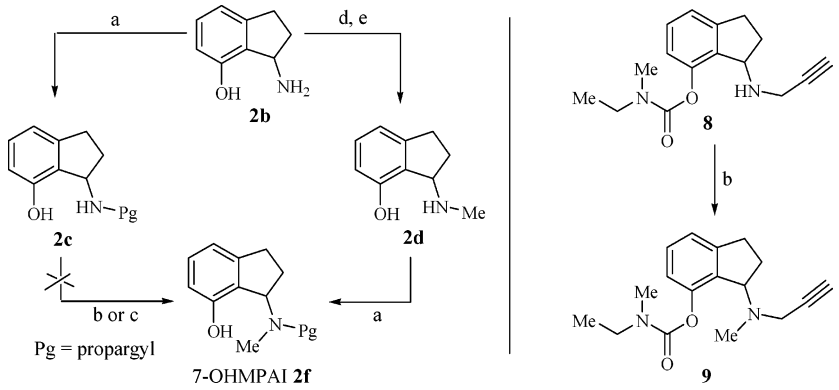
SCHEME 3. Preparation of *N*-Methyl Derivatives of 7-OHMPAI 2f and Carbamate 8[a]



[a] Reaction conditions: (a) propargyl bromide, MeCN, or dimethylacetamide; (b) $NaCNBH_3$, $(CH_2O)_n$, MeOH; (c) MeI, MeOH; (d) HCO_2Et, reflux; (e) $LiAlH_4$.

amino-8-hydroxy naphthalene **7**, six pK_a units stronger than 1-naphthol, was attributed by Awwal and Hibbert[17] to the presence of the intramolecular O- -H- -N bonds.

In fact, preparation of the few *N*-alkyl-7-OHAIs reported in the literature invariably involved reductive amination of indanones[4,13] and not reductive alkylation of aminoindans. Moreover, the authors specifically noted that 7-hydroxy-*N*,*N*-dipropyl-aminoindan was not "directly accessible from the amine", in contrast to non-OH analogues.[13]

As the synthesis of **2f** by the usual sequence involving the methylation of **2c** proved unsuccessful, the order of the alkylations was reversed, namely, **2b** was first *N*-methylated by formylation with ethyl formate, followed by $LiAlH_4$ reduction, to provide **2d**. No problem was found in this sequence, as the reaction took place in neat ethyl formate in the absence of either MeOH or a basic species. The final product **2f** was obtained by propargylation of **2d**. This mode of introducing a Me group was not applicable to **2c** because the subsequent $LiAlH_4$ reduction step was not compatible with the propargyl moiety. In contrast, *N*-methylation of the 7-carbamoyl-PAI **8** with $NaCNBH_3/(CH_2O)_n$ proceeded smoothly to afford **9**.[3] Also, the N−H group in **8** may be H-bonded to the carbamate oxygen, thus rendering the nitrogen more nucleophilic (Scheme 3).

Preliminary attempts to prepare the elusive 5-OHAI (**11**) and its propargyl derivative proved unsuccessful (Scheme 4). Thus, attempts to demethylate **10d**[18] under mild conditions (BBr_3, −5 °C) led to its degradation (large number of unidentified products) and did not afford the OH product. Likewise, demethylation of **10e** ($AlCl_3$, toluene, 60 °C) resulted in a compound lacking the familiar aminoindan NMR characteristics.

Compound **11**, reported by Oshiro et al.[4b] to be unstable, and its *N*-Me derivative **10c**, as well as the 5,6-dihydroxy-*N*-Me aminoindan **16**,[19] were eventually synthesized and isolated as their HCl salts, which, unlike the free bases, were found to be stable (Schemes 5 and 6).

When the hydrochlorides of compounds **10c** and **11**, which are unstable as free bases, were heated in the presence of MeOH/K_2CO_3, the methoxy derivative **17** was obtained. Heating in the nonnucleophilic acetonitrile in the presence of K_2CO_3 afforded the 5-hydroxy-indene **18**,[20] whereas in the absence of base, no reaction took place. Attempted base-catalyzed propargylation failed (Scheme 7).

The formation of **4a**, **4b**, and **4c** during the attempted reductive methylation of **2b** or **2c** (Scheme 2); the inability to prepare **2f** from **2c** by reductive alkylation and the successful methylation of **8** (Scheme 3); all the unsuccessful reactions described in Scheme 4; as well as the formation of compounds **17** and **18** and the stability of **10c** and **11** in the absence of base (Scheme 8) may stem from the intrinsic instability of the 5- and 7-OHAIs, attributed to facile formation of the corresponding QMs **19** and **20** obtained upon the elimination of ammonia or an amine in the 5- and 7-hydroxy aminoindans (Scheme 8). The base-catalyzed formation of compound **18** is attributed to the formation of the *para*-QM, followed by deprotonation and aromatization.

This putative mechanism resembles the well-documented self-immolative connector concept in prodrugs, which undergo spontaneous fragmentation to afford the parent drugs and QMs **22** and **24**. This approach was used, inter alia, for the synthesis of two doxorubicin prodrugs (Scheme 9).[21]

Although the 5-hydroxy-propargylated aminoindan (**10f**) was not accessible (Scheme 4), we succeeded in preparing carbamoyl derivatives of 5-OHAI (Scheme 10). Thus, the OH group of **10a**[22] was first carbamoylated to give **25a**, followed by reductive amination of the ketone under conditions compatible with the carbamoyl moiety to give **25d.** The carbamoyl functionality cannot donate electrons to the aromatic ring system, and, thus, no QM is formed. Propargylation of **25d** afforded **25**, a regioisomer of ladostigil. In contrast, attempts to prepare the analogous ester **25c** proved unsuccessful due to the instability of **25b** under the reaction conditions, where the ester, unlike the carbamate, underwent facile methanolysis to the 5-OH

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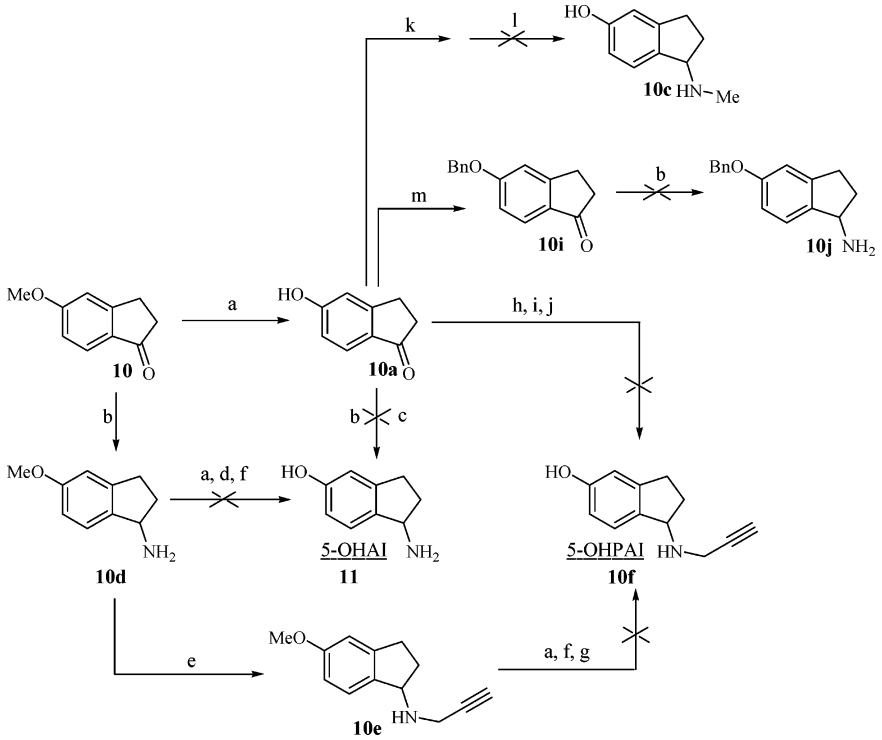
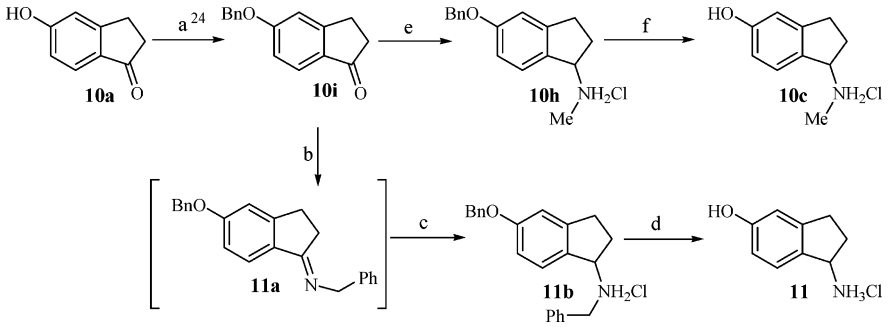
SCHEME 4. Unsuccessful Attempts to Prepare 10f[a]



[a] Reaction conditions: (a) $AlCl_3$, toluene; (b) $NaCNBH_3$, NH_4OAc; (c) NH_2OH, HCl; (d) HBr, HOAc; (e) propargyl bromide; (f) BBr_3; (g) H_2SO_4; (h) propargyl amine, $Na(OAc)_3BH$, rt, 5 days; (i) propargyl amine, $Na(OAc)_3BH$, HOAc, 55 °C, 24 h; (j) propargyl amine, $NaCNBH_3$, MeOH, rt; (k) $MeNH_2$; (l) H_2, Pd/C; (m) BnCl, K_2CO_3.

SCHEME 5. Preparation of the 5-OHAI Hydrochloride 11[a]



[a] Reaction conditions: (a) BnCl, K_2CO_3; (b) $BnNH_2$, TsOH; (c) (1) $NaBH_4$, MeOH, (2) HCl; (d) H_2, 10% Pd/C, MeOH, 24 h, rt; (e) $MeNH_2$, $NaCNBH_3$; (f) H_2, 10% Pd/C.

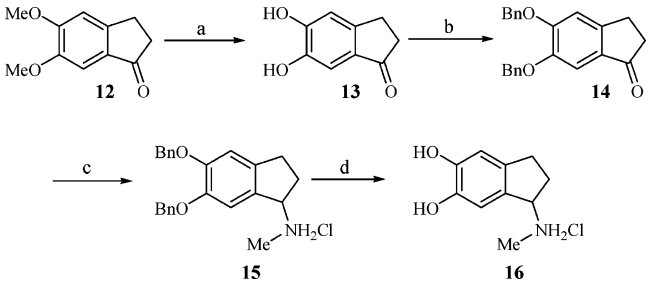
indanone (**10a**), which in turn was converted into 5-OHAI (**11**), stable only as its hydrochloride salt.

To evaluate whether the instability of the 5- and 7-OHAIs stems from their facile conversion into reactive QM intermediates, the presence of which usually can only be deduced from trapping studies, the following experiments were conducted.

2-Aminomethyl phenol **26**, as a monocyclic model of **2b**, was used in our initial studies on the formation and trapping of the QM intermediates (Scheme 11).

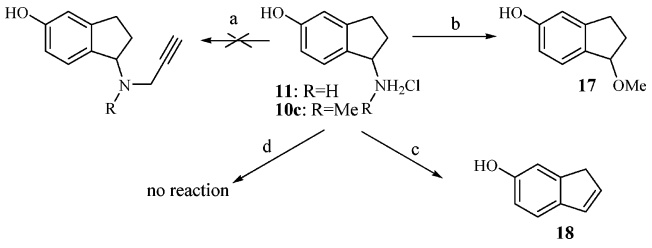
The products obtained in these experiments (Scheme 11) showed that **26** underwent thermal elimination to give the *ortho*-QM, which subsequently reacted as a Michael acceptor in the presence of a nucleophile. Although the reactions described were carried out in a nucleophilic solvent, the QM intermediate that formed preferentially reacted with another molecule of **26**, the best nucleophile present in the reaction mixture, leading to the formation of **27**, labeled as "symmetrical addition product" (SAP). When the reaction was carried out at 120 °C in a sealed pressure tube, the intermediate reacted with the solvent (ethanol)

SCHEME 6. Preparation of the 5,6-Dihydroxy-*N*-methyl-1-aminoindan Hydrochloride 16[a]



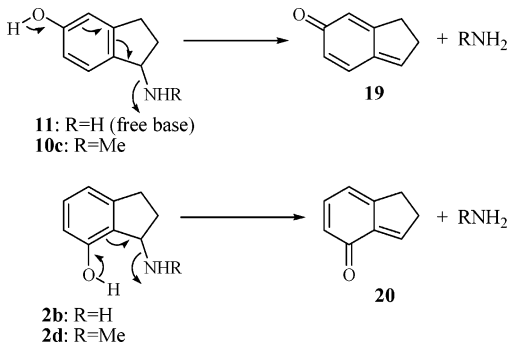
[a] Reaction conditions: (a) $AlCl_3$, toluene; (b) BnCl, K_2CO_3, DMF; (c) $MeNH_3Cl$, $NaCNBH_3$, THF/MeOH; (d) H_2, Pd/C, MeOH.

SCHEME 7. Degradation of 5-OHAIs[a]

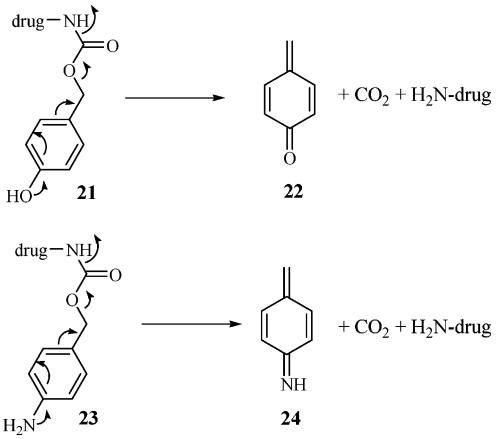


[a] Reaction conditions: (a) propargyl amine, K_2CO_3; (b) MeOH, K_2CO_3, heat; (c) MeCN, K_2CO_3, heat; (d) MeCN, heat.

SCHEME 8. Quinone Methides of 5- and 7-OHAIs



SCHEME 9. Self-Immolative Mode of Action of Doxorubicin Prodrugs



to provide **28** as the only product in a temperature-dependent yield. When benzylamine was treated under the same conditions, no products of displacement or condensation were observed, and the benzylamine remained intact. This observation suggests that the presence of the *o*-hydroxyl group plays a key role in these reactions.

Because *ortho*-QMs behave as heterodienes, another possible trapping course is the Diels−Alder reaction.[23] A QM, being an "inverse electron demand diene" in Diels−Alder reactions, requires electron-rich dienophiles, such as EVE.[24] Heating a neat mixture of **26** and EVE in a pressure tube at 140 °C led to the Diels−Alder adduct **30**, while at 100 °C, it gave a mixture of **30** as a minor product together with the tertiary amine **31** as a major component that was not isolated, but the structure of which was established by ^{1}H NMR (Scheme 12).

Compound **30** is a bicyclic acetal possessing an asymmetric carbon center, and the cyclohexene ring was expected to be in equilibrium of two possible conformers (Scheme 13).[25] However, its ^{1}H NMR spectrum, based on acetal-proton multiplicity, showed the presence of **A** as a sole conformer, where the ethoxy group is found at an axial position with no evidence for the presence of conformer **E**. The spectrum showed the acetal proton as a triplet with a coupling constant of 3.9 Hz, which is possible only when the proton is found in an equatorial position ($J_{HHa} = J_{HHb} = 3.9$ Hz). The prevalence of conformer **A** may be due to the anomeric effect, which contributes to the relative stability of this regioisomer.

After succeeding in trapping the intermediate obtained from the 2-aminomethyl phenol (**26**) model compound, the analogous reaction was repeated with 7-hydroxy-1-aminoindan (**2b**).[4b] Unlike the benzylic amine **26**, aminoindan **2b**, when refluxed in nucleophilic solvents (MeOH or EtOH), gave primarily ethers **4b** and **4b′**[14b] and a minor amount of the SAP product **4c** (Scheme 2). In the nonnucleophilic acetonitrile, the SAP product **4c** formed as a 2:1 mixture of a major (**M**) and a minor (**m**) diastereomers, which were not separated. The difference in the products obtained from **26** and **2b** may be attributed to the relative reactivity of their respective *ortho*-QM intermediates. Thus, the monocyclic intermediate **29**, obtained from **26**, appeared to be less reactive and more selective than the corresponding bicyclic intermediate **20**, obtained from **2b**. Whereas in the former case of intermediate **29**, the SAP product was that derived from selective nucleophilic addition of **26** to **29**, and in the latter case, intermediate **20** reacted rapidly with the alcoholic solvent present in large excess to give **4b** or **4b′**. The higher reactivity of the bicyclic *ortho*-QM intermediate **20** may stem from the cyclopentene ring strain, enabling it to react with the alcoholic solvent.

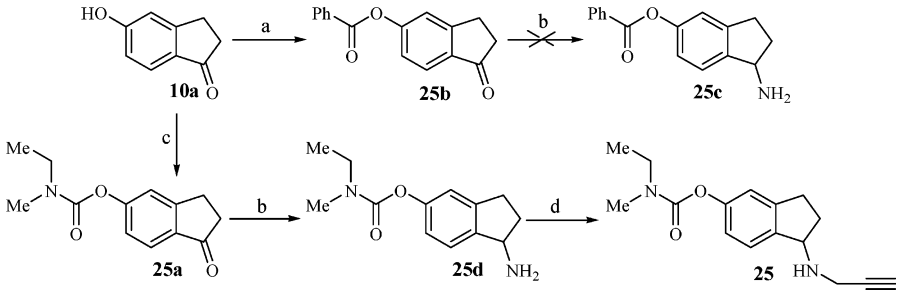
The *ortho*-QM intermediate **20** was also trapped by a similar Diels−Alder reaction, leading to a 1.5:1 mixture (^{1}H NMR) of novel tricyclic acetals **32a** and **32b**, obtained by exo and endo additions, respectively (Scheme 14). The structural determination of **32a** and **32b** was based on the multiplicity and coupling constants of the protons attached to both of the asymmetric carbons (Figure 4, models created with Symapps 6).

An analogous tetracyclic acetal **35**, obtained by photolysis of hydroxy-9-fluorenol (**33**) in the presence of EVE, has been reported (Scheme 15).[26]

The acetal protons in the ^{1}H NMR spectrum of **32a** and **32b** appeared as two neighboring multiplets, one as a triplet and the other as a double-doublet. The triplet multiplicity of the hydrogen is possible when found at an equatorial position so that it is gauche to both of its neighboring protons. According to this observation, the hydrogen displaying a triplet multiplicity belongs to the **32a** stereoisomer. Moreover, the axial position of the EtO group contributes to the relative stability of this conformer by involving the anomeric effect. The proton displaying a double-doublet multiplicity belongs to the stereoisomer **32b**, where the acetal proton is at an axial position being anti to one of its neighboring hydrogens and gauche to the other. The *H*-C9 appears as a triplet of triplets in both regioisomers **32a** and **32b**. The coupling constants correspond to the hydrogen located at a pseudoaxial position to both rings (Figure 4).

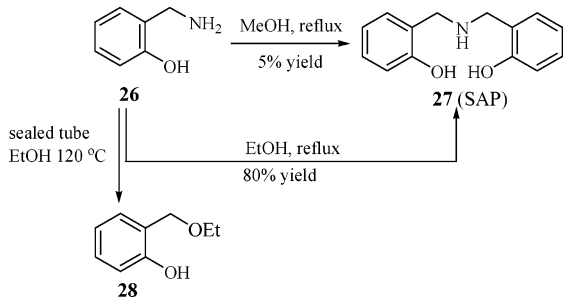
(23) Hall, H. K., Jr.; Rasoul, H. A. A.; Gillard, M.; Abdelkader, M.; Nogues, P.; Sentman, R. C. *Tetrahedron Lett.* **1982**, *23*, 603−606.
(24) Goldschmidt, Z.; Levinger, S.; Gottlieb, H. E. *Tetrahedron Lett.* **1994**, *35*, 7273−7276.
(25) Descotes, G.; Martin, J. C.; Mathicolonis, N. *Bull. Soc. Chim. Fr.* **1972**, 1077−1084.
(26) Fischer, M.; Shi, Y.; Zhao, B.; Snieckus, V.; Wan, P. *Can. J. Chem.* **1999**, *77*, 868−874.

SCHEME 10. Preparation of Carbamates 25 and 25d[a]

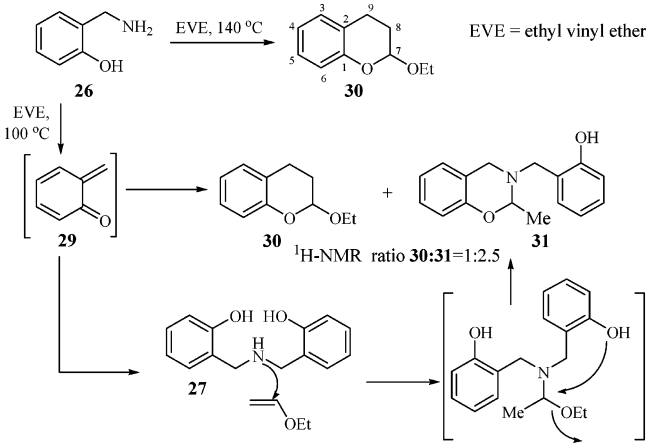


[a] Reaction conditions: (a) PhCOCl; (b) $NaCNBH_3$, NH_4OAc, MeOH; (c) ethyl-methyl carbamoyl chloride, K_2CO_3, CH_3CN; (d) propargyl bromide, K_2CO_3, CH_3CN.

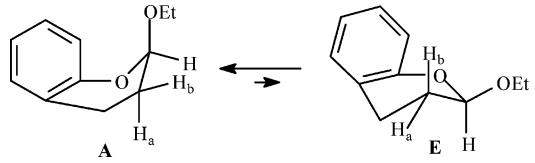
SCHEME 11. Degradation of 2-Aminomethyl Phenol 26



SCHEME 12. Trapping of QM 29 via a Diels−Alder Reaction



SCHEME 13. Equilibrium of 30 Conformers



When the 1.5:1 diastereomeric mixture of **32a** and **32b**, obtained from **2b**, was dissolved in $CDCl_3$, it underwent epimerization at the acetal carbon, shifting the ratio of **32a** and **32b** to 6:1. This observation supports the assumption that **32a** is the predominant product due to the anomeric effect.

Conclusions

The position of the OH group and its orientation relative to that of the amino moiety in hydroxy-aminoindans and their *N*-propargyl analogues was found to strongly affect their chemical stability and reactivity. Thus, the 4- and 6-OH regioisomers were found to be stable, while the 5-OH analogues were found to be inherently unstable as the free bases, and they could be isolated only as their HCl salts. 7-OHAI and 7-OHPAI represent an intermediate case, while sufficiently stable even as free bases, they exhibit, under certain experimental conditions, unexpected reactivity. The instability of the 5- and 7-hydroxy-aminoindans is attributed to their facile conversion to the corresponding, reactive QM intermediates, which readily react with nucleophiles to provide different types of addition products. The presence of the QM obtained from **2b** (7-OHAI) was established upon its trapping with EVE to give the tricyclic acetals **32a**,**b**.

Experimental Section

All commercial chemicals and solvents were reagent grade and were used without further purification, unless otherwise specified. Melting points are uncorrected. Silica gel 60 F254 plates were used for analytical TLC (visualized with UV light and iodine vapors); flash column chromatography was performed on silica gel 60 (70−230 mesh). Chemical shifts are expressed in δ (ppm) relative to TMS (in DMSO-d_6 or $CDCl_3$) as internal standard, or to HOD (4.80 ppm, in D_2O), and coupling constants (J) are in Hz. Reaction conditions were not optimized. The 4-, 6- and 7- OHAIs, OHPAIs and OHMPAIs were prepared as previously reported.[5] Spectroscopic data for compounds **10**,[27] **10a**,[22] **10d**,[18] **10i** (Scheme 4),[28] **12**,[29] **13**,[30] **14**,[19] **15**,[19] **16** (Scheme 6)[19] and **18**[20] (Scheme 7) have been previously described in the literature.

7-Hydroxy-indan (4a).[14a] A mixture of **2b**[4b,5] free base (1.0 g), paraformaldehyde (0.8 g), and $NaCNBH_3$ (0.44 g) in MeCN (20 mL) was heated at reflux under Ar for 5 h. The solvent was removed, and the yellow solid residue (2.4 g) was purified by flash column chromatography (hexane/EtOAc, 4:1) to give 110 mg of **4a.**

1-Methoxy-7-hydroxy-indan (4b) and *N*,*N*-Bis-(7-hydroxy-indan-1-yl)amine (4c). Method A: A solution of **2b** free base (1.5 g) in MeOH (40 mL) was heated at reflux under Ar for 20 h. The solvent was removed, and the residue (brown oil, 1.25 g) was purified by flash column chromatography (hexane/EtOAc, 3:1) to

(27) (a) Noureldin, N. A.; Zhao, D.; Lee, D. G. *J. Org. Chem.* **1997**, *62*, 8767−72. (b) Ohkata, K.; Akiyama, M.; Wada, K.; Sakaue, S.; Toda, Y.; Hanafusa, T. *J. Org. Chem.* **1984**, *49*, 2517−2520.

(28) Miyake, A.; Itoh, K.; Tada, N.; Tanabe, M.; Hirata, M.; Oka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2329−2348.

(29) (a) Garnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804−4807. (b) Haadsma-Svensson, S. R.; Cleek, K. A.; Dinh, D. M.; Duncan, J. N.; Haber, C. L.; Huff, R. M.; Lajiness, M. E.; Nichols, N. F.; Smith, M. W.; Svensson, K. A.; Zaya, M. J.; Carlsson, A.; Lin, C. H. *J. Med. Chem.* **2001**, *44*, 4716−4732.

(30) Gazit, A.; Osherov, N.; Posner, I.; Yaish, P.; Poraduso, E.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1991**, *34*, 1896−1907.

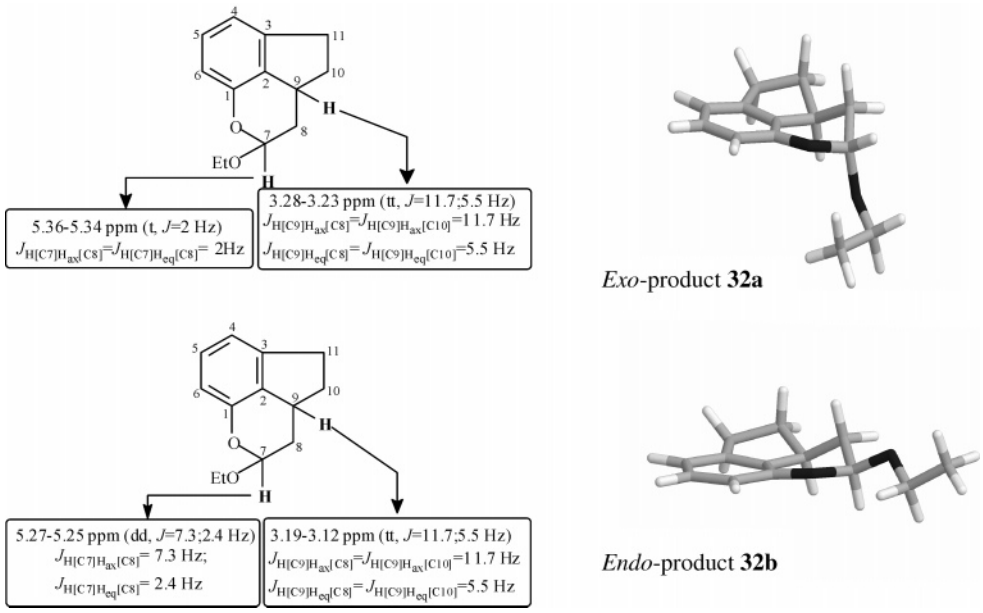
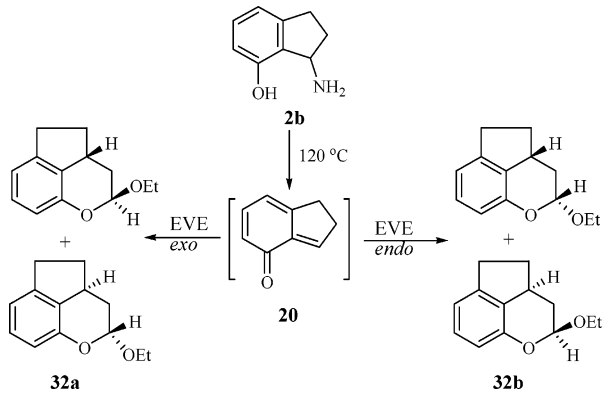
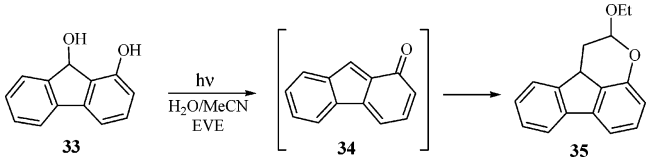


FIGURE 4. ^{1}H NMR evaluation of **32a**,**b**.

SCHEME 14. Diels−Alder Trapping Reaction of QM 20



SCHEME 15. Diels−Alder Trapping Reaction of Fluorenol 33



give 700 mg of **4b** and 400 mg of dimer **4c** (∼1:1 diastereomeric mixture, peak assignment based on full analysis of two-dimensional spectra). **Spectroscopic Data for 4b:** ^{1}H NMR (DMSO-d_6) δ 7.07−6.99 (t, 1H, J = 7.5 Hz, *H*-C5), 6.69−6.67 (d, 1H, J = 7.5 Hz, *H*-C4), 6.62−6.59 (d, 1H, J = 7.5 Hz, *H*-C6), 4.85−4.82 (dd, 1H, J = 4.7, 3.5 Hz, *H*-C1), 3.2 (s, 3H, OCH_3), 3.00−2.88 (dt, 1H, J = 16.4, 8 Hz, *H*-C3), 2.77−2.62 (ddd, 1H, J = 16.4, 8, 3.5 Hz, *H*-C3), 2.09−2.00 (m, 2H, *H*-C2). ^{13}C NMR (DMSO-d_6) δ 154.6 (C7), 146.8 (C9), 129.8 (C5), 128.6 (C8), 115.2 (C4), 113.0 (C6), 80.8 (C1), 55.7 (OCH_3), 31.4 (C2), 30.3 (C3). MS (CI/NH_3) *m*/*z* 164 (M^+, 19), 148 ([M − CH_3]$^+$, 17), 132 ([M − CH_3OH], 86). **Spectroscopic Data for 4c:** (mixture of diastereomers *RR*/*RS* [**M** = major, **m** = minor], peak assignment based on full analysis of two-dimensional spectra). ^{1}H NMR (DMSO-d_6) δ 7.03−7.01 (t, 2H, J = 7.2 Hz, *H*-C5 of **M**), 7.01−6.98 (t, 2H, J = 7.2 Hz, *H*-C5 of **m**), 6.69−6.68 (d, 2H, J = 7.2 Hz, *H*-C4 of **M**), 6.65−6.64 (d, 2H, J = 7.2 Hz, *H*-C4 of **m**), 6.55−6.53 (d, 2H, J = 7.2 Hz, *H*-C6 of **M**), 6.53−6.52 (d, 2H, J = 7.2 Hz, *H*-C6 of **m**), 4.48−4.46 (t, 2H, J = 6.6 Hz, *H*-C1 of **M**), 4.45−4.43 (t, 2H, J = 6.6 Hz, *H*-C1 of **m**), 2.95−2.91 (ddd, 2H, J = 15, 8, 4 Hz, *H*-C3 of **M**), 2.92−2.86 (m, 2H, *H*-C3 of **m**), 2.78−2.72 (ddd, 2H, J = 15, 8, 8 Hz, *H*-C3 of **M**), 2.68−2.63 (m, 2H, *H*-C3 of **m**), 2.52−2.46 (m, 2H, *H*-C2 of **M**), 2.42−2.35 (m, 2H, *H*-C2 of **m**), 1.89−1.83 (m, 4H, *H*-C2 of **M**/**m**). ^{13}C NMR (DMSO-d_6) δ 154.9 (C7 of **m**), 154.6 (C7 of **M**), 144.3 (C9 of **M**), 144.0 (C9 of **m**), 129.9 (C8 of **m**), 129.1 (C8 of **M**), 128.8 (C5 of **M**), 128.5 (C5 of **m**), 115.2 (C4 of **M**), 115.0 (C4 of **m**), 112.7 (C6 of **M**), 112.6 (C6 of **m**), 61.4 (C1 of **m**), 59.4 (C1 of **M**), 34.5 (C2 of **m**), 33.2 (C2 of **M**), 30.3 (C3 of **m**), 30.2 (C3 of **M**). MS (ES^-) *m*/*z* 280 ([M − H]$^-$, 100).

Method B: A mixture of **2c** free base (8.5 g), paraformaldehyde (6 g), and $NaCNBH_3$ (3.30 g) in anhydrous MeOH (150 mL) was heated at reflux under Ar for 4 h. The solvent was removed, and the yellow solid residue (16 g) was purified by flash column chromatography (hexane/EtOAc, 7:3) to give 6.1 g of a yellow oil. Of the latter, 3.3 g was further purified by flash column chromatography (CH_2Cl_2) to give **4a** (210 mg) and **4b** (880 mg).

1-Ethoxy-7-hydroxy-indan (4b′).[14b] A solution of **2b** free base (0.5 g) in EtOH (30 mL) was heated at 65 °C under Ar for 20 h. The solvent was removed, and the yellow oil residue (640 mg) was purified by flash column chromatography (hexane/EtOAc, 6:1) to give 180 mg of **4b′**. ^{1}H NMR (DMSO-d_6) δ 7.07−6.99 (t, 1H, J = 7.3 Hz), 6.69−6.61 (d, 1H, J = 7.3 Hz), 6.59−6.52 (d, 1H, J = 7.3 Hz), 4.93−4.9 (t, 1H, J = 3.5 Hz), 3.54−3.46 (m, 2H), 2.98−2.90 (dd, 1H, J = 16, 8 Hz), 2.70−2.62 (dt, 1H, J = 16, 5 Hz), 2.03−1.99 (m, 2H), 1.08−1.04 (t, 3H, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6) δ 154.5, 146.7, 129.6, 129.0, 115.3, 113.0, 79.2, 63.3, 32.0, 30.4, 15.6. MS (CI/NH_3) *m*/*z* 196 (MNH_4^+, 9), 178 (M, 29), 149 ([M − C_2H_5], 100), 131 ([M − C_2H_6O]$^+$, 100).

2,3-Dihydro-5-methoxy-1*H*-inden-1-amine Hydrochloride (10d).[31] A mixture of dry (evaporated 3 times from MeOH) ammonium acetate (54.3 g, 0.7 mol), 5-methoxy-1-indanone (**10**;[27] 10.0 g, 0.06 mol), and $NaCNBH_3$ (6.54 g, 0.1 mol) in dry MeOH (300 mL) was stirred and heated at reflux under nitrogen for 6 h. The mixture was cooled to 5 °C and acidified with concentrated HCl to pH of 1. The solvent was removed at reduced pressure to give an off-white solid. Ether (150 mL) was added, and the mixture was stirred for 20 min. The ether was decanted, and the process was repeated with another portion (150 mL) of ether. The yellow solid residue was dried under vacuum for 2 h and then dissolved

(31) Panetta, C. A.; Bunce, S. C. *J. Org. Chem.* **1961**, *26*, 4859−4866.

in a mixture of 25% aqueous NH_4OH (200 mL), water (100 mL), and CH_2Cl_2 (150 mL). The layers were separated, and the aqueous layer was re-extracted with CH_2Cl_2 (6 × 70 mL). The combined organic layer was dried over Na_2SO_4 and filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH 3:1) to give 4.08 g (40.6% yield) of the free base as a tan oil. This oil (1.2 g, 7.35 mmol) was dissolved in a mixture of dry ether (30 mL) and MeOH (50 mL), and ether saturated with HCl gas (14 mL) was added. The mixture was stirred at room temperature for 30 min, and the solvent was evaporated to give a white solid. Dry ether (130 mL) was added, and the mixture was stirred and filtered. Drying at 60 °C under vacuum for 60 h gave the title product as a white solid (1.10 g, 75%), mp 229−230 °C. ^{1}H NMR (D_2O) δ 7.45−7.42 (d, 1H, J = 8.4 Hz), 7.01 (d, 1H, J = 2.5 Hz), 6.96−6.92 (dd, 1H, J = 8.4, 2.5 Hz), 4.8−4.79 (m, 1H), 3.85 (s, 3H), 3.14−3.09 (m, 1H), 3.01−2.98 (m, 1H), 2.63−2.6 (m, 1H), 2.19−2.13 (m, 1H).

2,3-Dihydro-5-methoxy-*N*-(prop-2-ynyl)-1*H*-inden-1-amine Hydrochloride (10e).[31] A mixture of **10d** free base (2.02 g, 12.38 mmol) and K_2CO_3 (1.82 g, 13.17 mmol) in MeCN (50 mL) was stirred at room temperature under nitrogen for 20 min. A solution of propargyl bromide (1.33 g, 11.18 mmol) in MeCN (10 mL) was added dropwise with stirring under nitrogen over 15 min. After being stirred for 22 h, the mixture was filtered and the solvent was evaporated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give 1.3 g (58% yield) of the free base as a tan oil. This oil (0.75 g, 3.73 mmol) was dissolved in a mixture of dry ether (50 mL), and ether saturated with HCl gas (6 mL) was added. A gummy solid formed, and the mixture was stirred at room temperature for 20 min. The ether was decanted, a fresh portion of ether (50 mL) was added, and stirring was continued for 20 more minutes. The process was repeated with another portion (50 mL) of ether. The precipitated white solid was filtered and dried under vacuum at 60 °C for 48 h to give the title product as a white solid (650 mg, 73%), mp 122−124 °C. ^{1}H NMR (D_2O) δ 7.49−7.46 (d, 1H, J = 8.4 Hz), 7.03−7.02 (d, 1H, J = 2.2 Hz), 6.96−6.92 (dd, 1H, J = 8.4, 2.2 Hz), 4.92−4.88 (dd, 1H, J = 7.6, 2.5 Hz), 3.95−3.93 (t, 2H, J = 2.4 Hz), 3.85 (s, 3H), 3.18−3.12 (m, 1H), 3.09−2.99 (m, 2H, *H*-C3), 2.62−2.54 (m, 1H), 2.33−2.28 (m, 1H).

Benzyl-(5-bezyloxy-indan-1-ylidene)-amine (11a).[32] A mixture of **10i**[28] (2.5 g, 10.5 mmol), benzylamine (1.26 g, 11.8 mmol), *p*-toluenesulfonic acid monohydrate (0.60 g, 3.15 mmol), and dry toluene (150 mL) was stirred and heated at reflux for 5 h while removing the water formed by means of a Dean−Stark trap. The mixture was cooled to 25 °C, and the insoluble material was filtered off. The filtrate was evaporated at reduced pressure to give a residue shown by TLC to consist of a mixture of unreacted **10i** (∼40%) and compound **11a** (∼60%). The residue was used in the next step without further purification.

***N,O*-Dibenzyl-5-hydroxy-1-aminoindan Hydrochloride (11b).**[32] The residue from the previous step was dissolved in MeOH (150 mL), and $NaBH_4$ (600 mg, 15.9 mmol) was added portionwise under ice cooling. After stirring at 25 °C for 1 h under N_2, the mixture was poured into cold water (70 mL) and extracted with CH_2Cl_2 (6 × 70 mL). The combined organic phase was washed with water (150 mL), dried (Na_2SO_4), and evaporated. The residue was dissolved in a mixture of anhydrous ether (25 mL) and CH_2Cl_2 (5 mL), and ether saturated with HCl gas (10 mL) was added with stirring. A dark solid precipitated, and the solvent was decanted. Dry ether (100 mL) was added to the solid, and the mixture was stirred for 30 min and filtered. The solid was again treated with dry ether (100 mL) and stirred for 30 min, and the suspension was filtered to give 2.5 g of a tan solid. This crude material was purified by stirring it with EtOAc (30 mL) for 20 min and filtering under vacuum. The above washings with EtOAc were repeated two more times to give 2.2 g of a light tan solid (57% from **10i**), mp 186−188 °C. ^{1}H NMR (D_2O) δ 7.59−7.57 (d, 1H, J = 6 Hz), 7.52−7.5 (d, 2H, J = 5.2 Hz), 7.29−7.19, 7.62 (m, 8H), 6.74−6.71 (m, 2H, *H*-C4), 4.84 (d, 2H, J = 1.4 Hz), 4.29−4.26 (dd, 1H, J = 5.7, 2.2 Hz), 3.72 (s, 2H), 3.23−3.15 (dt, 1H, J = 12.1, 5.9 Hz), 2.75−2.67 (ddd, 1H, J = 12.1, 6.6, 2.7 Hz), 2.34−2.28 (m, 1H), 2.27−2.19 (m, 1H). MS (CI/NH_3) m/z 224 ([M − $PhCH_2OH$]$^+$, 100), 330 (MH^+, 52).

5-Hydroxy-1-aminoindan Hydrochloride (11). A mixture of **11b** (1.20 g, 3.3 mmol) in MeOH (200 mL) and 10% Pd/C catalyst (1.50 g) was hydrogenated at an initial pressure of 3.5 atm for 28 h. The mixture was then filtered through Celite, and the residue was washed with MeOH. Evaporation of the solvent at 35 °C gave 520 mg (85% yield) of a light tan solid. ^{1}H NMR (D_2O) δ 7.35−7.32 (d, 1H, J = 8.3 Hz), 6.85−6.84 (d, 1H, J = 2.2 Hz), 6.81−6.77 (dd, 1H, J = 8.3, 2.2 Hz), 4.72 (m, 1H), 3.33−2.95 (dt, 1H, J = 12.1, 8 Hz), 2.94−2.91 (ddd, 1H, J = 12.1, 9, 5 Hz), 2.57−2.51 (m, 1H), 2.14−2.08 (m, 1H). MS (CI/NH_3) m/z 150 (MH^+, 13), 132 ([M − NH_2]$^+$, 100). Anal. Calcd for $C_9H_{12}NOCl\cdot 0.75H_2O$: C, 54.28; H, 6.83; N, 7.03. Found: C, 54.45; H, 6.38; N, 7.26. HRMS (DCI/CH_4) m/z calcd for C9H11NO (M^+), 149.0841; found, 149.0815.

***O*-Benzyl-*N*-methyl-5-hydroxy-1-aminoindan Hydrochloride (10h).** A mixture of **10i** (3.45 g, 14.5 mmol), 8 M ethanolic methylamine (15 mL, 120 mmol), $MeNH_2$ hydrochloride (3.6 g, 53 mmol), $NaCNBH_3$ (1.47 g, 23.4 mmol), dry THF (375 mL), and MeOH (125 mL) was stirred and heated at reflux under N_2 for 8 h. The mixture was cooled to 5 °C and acidified to pH 1 with concentrated HCl. Evaporation at 45 °C gave a tan solid that was treated with CH_2Cl_2 (250 mL) and water (250 mL). The resulting mixture was separated, and the aqueous layer was re-extracted with CH_2Cl_2 (10 × 60 mL). The combined organic layer was washed with water (150 mL) and brine (150 mL) and dried (Na_2SO_4). Evaporation of solvent at reduced pressure gave a light tan solid that was purified by flash chromatography (CH_2Cl_2/MeOH, 4:1) to give 3.0 g of a light yellow solid. The solid was further purified by stirring it with hexane (50 mL) at 25 °C for 30 min and filtering. The hexane washing was repeated one more time to give 2.70 g (64%) of a yellowish solid, mp 174−176 °C. ^{1}H NMR ($CDCl_3$) δ 7.6−7.57 (d, 1H, J = 9.1 Hz), 7.31−7.2 (m, 5H), 6.8−6.78 (m, 2H), 4.91 (s, 2H), 4.48−4.44 (dd, 1H, J = 7.7, 3.2 Hz), 3.23−3.17 (m, 1H), 2.84−2.81 (m, 1H), 2.41−2.09 (m, 5H). MS (CI/NH_3) m/z 254 (MH^+, 20), 222 ([M − $NHCH_3$]$^+$, 100), 132 ($C_9H_{10}N$, 98).

***N*-Methyl-5-hydroxy-1-aminoindan Hydrochloride (10c).** A solution of **10h** (1.75 g, 6 mmol) in MeOH (200 mL) was hydrogenated in the presence of 10% Pd/C (550 mg) at 25 °C at an initial pressure of 3.5 atm for 2 h. The mixture was then filtered through filter-aid, and the residue was washed with MeOH. Evaporation of the solvent at 35 °C gave 1.16 g (96%) of an off-white solid. ^{1}H NMR (D_2O) δ 7.38−7.36 (d, 1H, J = 8.4 Hz), 6.85 (s, 1H), 6.82−6.79 (dd, 1H, J = 8.4, 2.1 Hz), 4.66−4.62 (dd, 1H, J = 7.8, 2.7 Hz), 3.15−3 (dt, 1H, J = 12, 8 Hz), 2.96−2.85 (ddd, 1H, J = 12, 6, 2.7 Hz), 2.67 (s, 3H), 2.58−2.4 (m, 1H), 2.3−2.15 (m, 1H). MS (CI/NH_3) m/z 164 (MH^+, 28), 132 ([M − CH_3NH_2], 100). Anal. Calcd for $C_{10}H_{14}NOCl\cdot H_2O$: C, 55.17; H, 7.41; N, 6.44. Found: C, 55.62; H, 6.84; N, 6.31. HRMS (DCI/CH_4) m/z calcd for C10H13NO (M^+), 163.0997; found, 163.0970.

1-Methoxy-5-hydroxy-indan (17). A mixture of 5-hydroxy-1-aminoindan hydrochloride (**11**; 300 mg, 1.50 mmol), K_2CO_3 (500 mg, 3.62 mmol), and MeOH (50 mL) was stirred and heated at reflux for 4.5 h. The mixture was cooled, silica gel (600 mg) was added, and the mixture was evaporated to give silica gel impregnated with the crude product, which was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:3) to give 150 mg (61%) of a yellow oil. ^{1}H NMR (DMSO-d_6) δ 9.29 (s, 1H), 7.13−7.11 (d, 1H, J = 8 Hz), 6.61 (s, 1H), 6.58−6.55 (dd, 1H, J = 8, 2.3 Hz), 4.63−4.6 (dd, 1H, J = 6.4, 3.2 Hz), 3.23 (s, 3H), 3.05−2.9 (m,

(32) Chromanyl Glycines. Oka, Y.; Nishikawa, K.; Miyake, A. US Patent 4,521,607, June 4, 1985.

1H), 2.78−2.64 (m, 1H), 2.31−2.26 (m, 1H), 2.16−2.11 (m, 1H). MS (CI/i-butane) *m*/*z* 163 (M^+, 17).

5-Hydroxy-1-indene (18).[20] A mixture of 5-hydroxy-1-aminoindan hydrochloride (**11**; 170 mg, 0.92 mmol), K_2CO_3 (306 mg, 2.21 mmol), and MeCN (75 mL) was stirred and heated at reflux for 4.5 h. The mixture was cooled, silica gel (550 mg) was added, and the mixture was evaporated to give silica gel impregnated with the crude product. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:3) to give 70 mg (58%) of an off-white solid.

Ethyl-methyl-carbamic Acid 1-Oxo-indan-5-yl Ester (25a). A mixture of **10a**[22] (2.5 g, 16.7 mmol), dry MeCN (100 mL), K_2CO_3 (4.6 g, 33.4 mmol), and *N*-methyl-*N*-ethyl-carbamoyl chloride (2.4 g, 20 mmol) was stirred and heated at reflux under N_2 for 6 h. The solvent was evaporated, and water (150 mL) and ether (150 mL) were added to the residue. The layers were separated, and the aqueous layer was re-extracted with ether (7 × 70 mL). The combined ether layer was washed with saturated $NaHCO_3$ and dried (Na_2SO_4). The solution was filtered, the solvent was evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 4:6) to give 3.60 g (92.5%) of a white solid, mp 59−61 °C. ^{1}H NMR (DMSO-d_6) δ 7.64−7.61 (d, 1H, J = 8.3 Hz), 7.32 (s, 1H), 7.16−7.13 (d, 1H, J = 8.3 Hz), 3.45−3.29 (q, 2H, J = 6.5 Hz), 3.09−3 (m, 2H), 2.9 (s, 3H), 2.65−2.61 (m, 2H), 1.2−1.08 (m, 3H).

Ethyl-methyl-carbamic Acid 1-Amino-indan-5-yl Ester Hydrochloride (25d). A mixture of dry NH_4OAc (13 g, 169 mmol; evaporated 3 times from MeOH), **25a** (2.83 g, 12 mmol), and $NaCNBH_3$ (1.3 g, 20.7 mmol) in dry MeOH (150 mL) was stirred and heated at reflux under N_2 for 9 h. The mixture was cooled to 5 °C and acidified to pH 1 with concentrated HCl. The solvent was evaporated to give a white semisolid. Ether (150 mL) was added, and the mixture was stirred for 20 min. The ether was decanted, and the process was repeated with another 150 mL portion of ether. The white semisolid was dried at room temperature under vacuum for 2 h. The white residual solid was then dissolved in a mixture of 25% aqueous NH_4OH (200 mL), water (75 mL), and CH_2Cl_2 (150 mL). The layers were separated, and the aqueous layer was re-extracted with CH_2Cl_2 (6 × 70 mL). The combined organic phase was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 3:1) to give 1.45 g (51%) of **25d** (free base) as a yellow oil. This oil (0.30 g, 1.3 mmol) was dissolved in a mixture of dry ether (50 mL) and MeOH (35 mL), and ether saturated with HCl gas (3 mL) was added. The mixture was stirred at room temperature for 30 min, and the solvent was evaporated to give a viscous oil. Dry ether (50 mL) was added, the mixture was stirred, and the ether was decanted. The process was repeated with another portion (50 mL) of ether. Drying of the residue at 50 °C under vacuum for 60 h gave **25d** as a white solid (260 mg, 75%), mp 97−103 °C. ^{1}H NMR (D_2O) δ 7.53−7.5 (d, 1H, J = 8.3 Hz), 7.13 (s, 1H), 7.09−7.06 (d, 1H, J = 8.3 Hz), 4.89−4.85 (dd, 1H, J = 7.9, 4.7 Hz), 3.56−3.35 (q, 2H, J = 6.4 Hz), 3.22−2.96 (m, 5H), 2.72−2.6 (m, 1H), 2.22−2.13 (m, 1H), 1.28−1.15 (m, 3H, J = 6.4 Hz). MS (CI/NH_3) *m*/*z* 235 (MH^+, 10), 218 ([M − NH_3], 100).

Ethyl-methyl-carbamic Acid 1-Prop-2-ynylamino-indan-5-yl Ester Hydrochloride (25). A mixture of **25d** free base (1.2 g, 5 mmol), K_2CO_3 (0.68 g, 4.95 mmol), and MeCN (100 mL) was stirred at room temperature under N_2 for 20 min. A solution of propargyl bromide (0.53 g, 4.5 mmol) dissolved in MeCN (12 mL) was added dropwise with stirring under N_2 over 15 min. After being stirred for 22 h, the mixture was filtered and the solvent was evaporated. The residue was purified by flash column chromatography (elution with EtOAc) to give 780 mg (65%) of **25** (free base) as a viscous yellow oil. This oil (0.78 g, 2.9 mmol) was dissolved in dry ether (50 mL), and ether saturated with HCl gas (7 mL) was added. A gummy solid formed, and the mixture was stirred at room temperature for 20 min. The ether was decanted, a fresh portion of ether (50 mL) was added, and stirring was continued for an additional 20 min. This ether was also decanted, and the process was repeated with another portion (50 mL) of ether. The precipitated white solid was filtered and dried to give **25** (700 mg, 79%), mp 168−170 °C. ^{1}H NMR (D_2O) δ 7.58 (d, 1H, J = 8.3 Hz), 7.16 (s, 1H), 7.11−7.08 (d, 1H, J = 8.3 Hz), 5.0−4.96 (dd, 1H, J = 7.65, 2.9 Hz), 3.99 (d, 2H, J = 0.72 Hz), 3.55−3.37 (q, 2H, J = 7.3 Hz), 3.19−2.99 (m, 6H), 2.65−2.6 (m, 1H), 2.37−2.29 (m, 1H), 1.27−1.15 (t, 3H, J = 7.3 Hz). MS (CI/NH_3) *m*/*z* 273 (MH^+, 12), 218 ([M − C_3H_4N], 100). Anal. Calcd for $C_{16}H_{20}N_2O_2$·HCl: C, 62.23; H, 6.86; N, 9.07; Cl, 11.48. Found: C, 61.83; H, 6.99; N, 9.09; Cl, 11.02.

2-Aminomethyl Phenol (26).[33] A mixture of salicyloxime (3 g, 22 mmol) and 5% Pd/C (0.5 g) in MeOH (50 mL) was hydrogenated at room temperature under 13 psi pressure, with vigorous stirring, for 4 h. The catalyst was filtered through Celite, and the filtrate was further purified by column chromatography (hexane/EtOAc, 1:1) to provide a colorless solid in 35% yield, mp 125−128 °C [lit[34] 128 °C]. ^{1}H NMR (DMSO-d_6) δ 7.05 (m, 2H), 6.70 (m, 2H), 3.85 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 157.0, 127.7, 127.3, 126.6, 118.0, 115.0, 43.0. MS (ES^+) *m*/*z* 230 ([$C_7H_7O]_2$NH, 100), 214 (MH^+, 10). HRMS (DCI/CH_4) *m*/*z* calcd for C_7H_9NO (M^+), 123.068414; found, 123.06642.

2-((2-Hydroxybenzylamino)methyl)phenol (27).[35] A solution of **26** (1 mmol) in EtOH (5 mL) was refluxed overnight and concentrated under reduced pressure to give a yellowish solid. Upon addition of MeOH, the residue precipitated as a white solid, which was filtered and dried to give **27** in 80% yield, mp 173−174 °C. Anal. Calcd for $C_{14}H_{15}NO_2$ (229.11): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.12; H, 6.67; N, 5.93.

2-(Ethoxymethyl)phenol (28).[36] A solution of **26** (1 mmol) in EtOH (5 mL) was heated at 120 °C in a sealed pressure tube for 8 h. After cooling, the solvent was concentrated to give **28** as a yellow-colored oil in quantitative yield. ^{1}H NMR (DMSO-d_6) δ 7.22−7.18 (dd, 1H, J = 5.8, 1.6 Hz), 7.11−7.03 (td, 1H, J = 8.2, 1.8 Hz), 6.81−6.72 (m, 2H), 4.40 (s, 2H), 3.53−3.42 (q, 2H, J = 7 Hz), 1.23−1.05 (t, 3H, J = 7 Hz). ^{13}C NMR (DMSO-d_6) δ 154.8, 129.6, 128.1, 124.8, 118.7, 114.9, 66.7, 65.0, 15.2. MS (ES^+) *m*/*z* 107 (C_7H_7O, 100), 153 (MH^+, 20).

2-Ethoxy-3,4-dihydro-2*H*-chromene (30)[37] and 2-((2-Methyl-2*H*-benzo[e][1.3]oxazin-3(4*H*)-yl)methyl)phenol (31). A solution of **26** (1 mmol) and EVE (5 mL) was heated in a sealed pressure tube at 140 °C overnight. After cooling, traces of EVE were evaporated to provide a yellow-colored residue, which consisted mainly of polymerized EVE. To this residue was added CH_2Cl_2, and the mixture was filtered through a short silica gel column. The filtrate was evaporated to dryness to give **30** as a colorless oil in 10% yield. ^{1}H NMR ($CDCl_3$) δ 7.20−7.08 (t, 1H, J = 8.1 Hz, *H*-C5), 7.08−7.00 (d, 1H, J = 7.4 Hz, *H*-C3), 6.90−6.70 (m, 2H, *H*-C6, *H*-C4), 5.20 (t, 2H, J = 3.9 Hz, *H*-C7), 3.90−3.80 (dq, 1H, J = 9.7, 7.1 Hz, O*CH*$_2$CH$_3$), 3.65−3.55 (dq, 1H, J = 9.7, 7.1 Hz, O*CH*$_2$CH$_3$), 3.05−2.90 (td, 1H, J = 12.7, 4.2 Hz, H_{ax}-C9), 2.60−2.50 (dt, 1H, J = 12.7, 5.6 Hz, H_{eq}-C9), 2.10−1.90 (m, 2H, H−C8), 1.20−1.10 (t, 3H, J = 7.1 Hz, OCH$_2$*CH*$_3$). ^{13}C NMR ($CDCl_3$) δ 156.1 (C1), 129.4 (C3), 127.4 (C5), 124.8 (C2), 120.7 (C4), 117.1 (C6), 99.0 (C7), 63.8 (O*CH*$_2$CH$_3$), 26.7 (C8), 20.7 (C9), 15.8 (OCH$_2$*CH*$_3$). MS (CI^+) *m*/*z* 107.03 (C_7H_7O, 100), 178.097 (MH^+, 100). HRMS (DCI/CH_4) *m*/*z* calcd for $C_{11}H_{14}O_2$ (MH^+), 178.099380; found, 178.097403. When the reaction was carried out at 100 °C, a mixture of **30** and **31** in a ratio of 1:2.5, as determined by ^{1}H

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NMR, was obtained. ^{1}H NMR of compound **31**, which was not isolated. ^{1}H NMR ($CDCl_3$) δ 7.25−7.15 (m, 2H), 6.93−6.8 (m, 6H), 5.15−5.11 (q, 1H, J = 6 Hz), 4.2−4.15 (d, 1H, J = 14.4 Hz), 4.02 (s, 2H), 3.88−3.85 (d, 1H, J = 14.4 Hz), 1.6−1.57 (d, 3H, J = 6 Hz).

2-Ethoxy-3,3a,4,5-tetrahydro-2*H*-cyclopenta(*de*)chromene (32a,b). A solution of **2b** (0.25 mmol) and EVE (3 mL) was heated in a sealed pressure tube at 120 °C overnight. After cooling, traces of EVE were evaporated to provide a yellow-colored residue, which consisted mainly of polymerized EVE. To the residue was added CH_2Cl_2, and the mixture was filtered through a short silica gel column. The filtrate was evaporated to dryness to give the desired product as colorless oil in 7% yield. ^{1}H NMR ($CDCl_3$) δ 7.08−7.05 (t, 1H, J = 7.8 Hz, *H*-C5 of **32a**), 7.05−7.03 (t, 1H, J = 7.8 Hz, *H*-C5 of **32b**), 6.83−6.82 (d, 1H, J = 7.8 Hz, *H*-C4 of **32a**), 6.77−6.76 (d, 1H, J = 7.8 Hz, *H*-C4 of **32b**), 6.63−6.62 (d, 1H, J = 7.8 Hz, *H*-C6 of **32a**), 6.61−6.59 (d, 1H, J = 7.8 Hz, *H*-C6 of **32b**), 5.36−5.34 (t, 1H, J = 2 Hz, H_{eq}-C7 of **32a**), 5.27−5.25 (dd, 1H, J = 7.3, 2.4 Hz, H_{ax}-C7 of **32b**), 4.14−4.08 (dq, 1H, J = 9.5, 7.2 Hz, O*CH*$_2$CH$_3$ of **32b**), 3.97−3.92 (dq, 1H, J = 9.5, 7.2 Hz, O*CH*$_2$CH$_3$ of **32a**), 3.68−3.63 (dq, 1H, J = 9.5, 7.2 Hz, O*CH*$_2$-CH$_3$ of **32a** and **32b**), 3.28−3.23 (tt, 1H, J = 11.7, 5.5 Hz, *H*-C9 of **32a**), 3.19−3.12 (tt, 1H, J = 11.7, 5.5 Hz, *H*-C9 of **32b**), 2.98−2.92 (ddd, 1H, J = 15, 11.7, 5.5 Hz, H_{ax}-C11 of **32a** and **32b**), 2.79−2.75 (dd, 1H, J = 15, 8 Hz, H_{eq}-C11 of **32b**), 2.78−2.74 (dd, 1H, J = 15, 8 Hz, H_{eq}-C11 of **32a**), 2.41−2.37 (dt, 1H, J = 11.7, 5.5 Hz, H_{eq}-C10 of **32a** and **32b**), 2.36−2.33 (ddd, 1H, J = 11.7, 5.5, 2 Hz, H_{eq}-C8 of **32b**), 2.33−2.30 (ddd, 1H, J = 11.7, 5.5, 2 Hz, H_{eq}-C8 of **32a**), 1.63−1.56 (qd, 1H, J = 11.7, 8 Hz, H_{ax}-C10 of **32a** and **32b**), 1.48−1.43 (td, 1H, J = 11.7, 2 Hz, H_{ax}-C8 of **32a** and **32b**), 1.31−1.29 (t, 3H, J = 7.2 Hz, OCH$_2$*CH*$_3$ of **32b**), 1.21−1.19 (t, 3H, J = 7.2 Hz, OCH$_2$*CH*$_3$ of **32a**). ^{13}C NMR ($CDCl_3$) δ 150.4 (C1 of **32a**/**32b**), 144.7 (C3 of **32a**/**32b**), 130.1 (C2 of **32a**/**32b**), 128.5 (C5 of **32b**), 128.1 (C5 of **32a**), 116.4 (C4 of **32a**), 116.2 (C4 of **32b**), 112.0 (C6 of **32a**), 111.9 (C6 of **32b**), 102.0 (C7 of **32b**), 98.2 (C7 of **32a**), 64.9 (O*CH*$_2$CH$_3$ of **32b**), 63.8 (O*CH*$_2$CH$_3$ of **32a**), 37.2 (C10 of **32b**), 35.2 (C10 of **32a**), 35.1 (C8 of **32b**), 33.2 (C8 of **32a**), 32.9 (C11 of **32b**), 32.4 (C11 of **32a**), 31.8 (C9 of **32a**), 29.7 (C9 of **32b**), 15.2 (OCH$_2$*CH*$_3$ of **32b**), 15.1 (OCH$_2$*CH*$_3$ of **32a**). No molecular peak was observed in the MS spectrum of compounds 32a,b.

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Supporting Information Available: ^{1}H or ^{13}C NMR spectra for **4a**, **4b**, **4b′**, **4c**, **10d**, **10e**, **10h**, **11b**, **17**, **18**, **25a**, **25d**, and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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