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Preparation of Sixteen 3-Hydroxy-4- and 7-Hydroxy-1-hydrindanones and 3-Hydroxy-4- and 8-Hydroxy-1-hydroazulenones

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3-Hydroxyoctahydro-4*H*-inden-4-ones and 7-hydroxyoctahydro-1*H*-inden-1-ones (**1**, **2** and **3**, **4**, respectively), as well as the homologous 3-hydroxyoctahydro-4(1*H*)-azulenones (**5**, **6**) and 8-hydroxyoctahydro-1(2*H*)-azulenones (**7**, **8**), were prepared diastereoselectively either from the precursor α,β-enones **9**, **10**, **11**, and **12** or by an isoxazoline method. Unmasking of the isoxazolines **13i**, **14i**, and **14j** with O_3 proved a more stereoselective process than hydrogenolysis. In many cases epimerization with 100 % completeness was observed on passing the epimerizable diastereomers once through a column filled with silica gel, the *trans*-fused hydrindanones thus in most cases furnishing the *cis*-fused epimers and the *cis*-fused hydroazulenones the *trans* forms. These results have been corroborated by AM1 theoretical computations, which indicate that the *cis*-fused epimers in these hydrindanone systems are more stable than the *trans*-fused variants, whereas the reverse was calculated for the hydroazulenone homologues.

Introduction

The hydroxyhydrindanone[1–4] (**1**–**4**) and -hydroazulenone[5,6] (**5**–**8**) skeletons are found incorporated in a plethora of natural products or intermediate compounds leading to them: characteristic examples are to be found among steroidal compounds,[1] alkaloids,[2] diterpenes,[3,5] and sesquiterpenes[4,6] (Figure 1). The synthesis of these and similar compounds, however, is occasionally complicated by epimerization at the juncture of the two rings, usually furnishing the more stable epimer – *cis* in hydrindanone[7] and *trans* in hydroazulenone[6l,7f,8] systems – as the predominant or exclusive product. Furthermore, during their preparation, many of these and related ketols suffer in situ dehydration to provide the corresponding α,β-enones **9**,[7b,8d,9] **11**,[6b,l,8d,9a,9j,10] **10**,[9j,11] and **12**,[3e,6o] or related enones containing **9**–**12** as subunits. In view of the importance of these systems in natural product synthesis and the aforementioned problems, we directed our attention toward the synthesis of the sixteen diastereomerically pure aldols **1**–**8**.

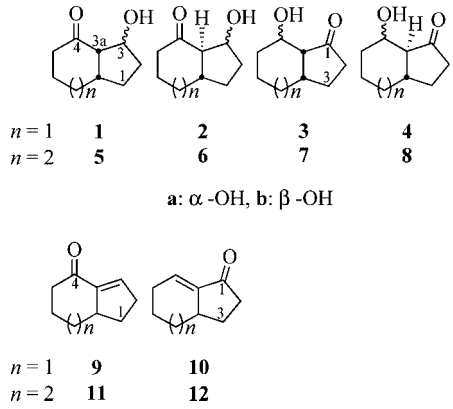

Figure 1. Hydroxyhydrindanones **1**–**4**, hydroxyhydroazulenones **5**–**8**, hydrindenones **9**, **10**, and hydroazulenones **11**, **12**.

Results and Discussion

Starting from the known[9a,9j] α,β-enones **9** and **11**, the aldols **1**, **2**, **5**, and **6** were each assembled in three to five simple steps by the sequence illustrated in Scheme 1. Protection of the carbonyl moiety in **9**, followed by hydroboration/oxidation,[12] furnished the acetalols **9b** and **9c**, which were conveniently separable by column chromatography on silica gel. From the product ratios, the preferred side of borane attack is the less hindered convex (β) side, by a factor of ca. two. Mild deacetalization of **9b** and **9c** afforded **1b** and **2a**. Preparation of the hydroazulenic aldols **5b** and **6a** was entirely analogous.

Swern[13] or PCC[14] oxidation of the hydroxy acetals **9b**, **9c**, **11b**, and **11c** to the keto acetals **9d**, **9e**, **11d**, and **11e**, followed by reduction with dibal-H, provided the hydroxy acetals **9f**, **9g**, **11f**, and **11g**, respectively, with notably high diastereoselectivities observed during the reduction steps. The *cis*-fused ketones exclusively furnished α-alcohols, whereas the *trans*-fused variants afforded the β-isomers,

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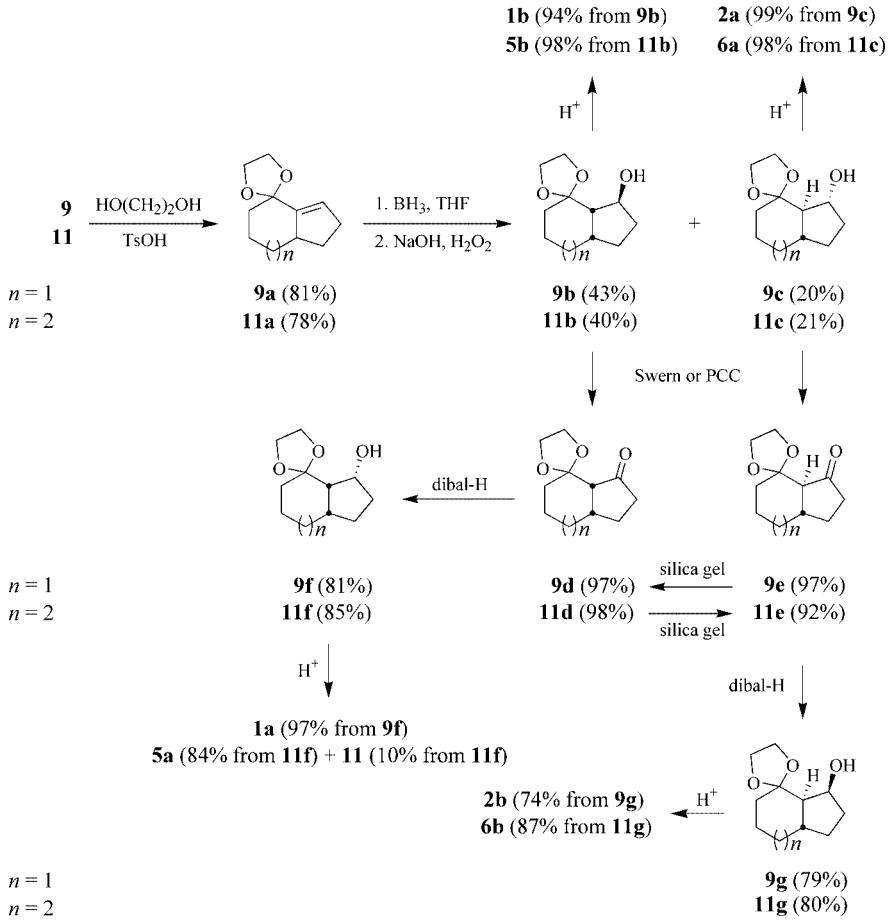


Scheme 1. Preparation of aldols **1**, **2**, **5**, and **6**.

which suggests that hydride transfer from dibal-H to the carbonyl group takes place from the less hindered β-face in the *cis* ketones, but from the α-face in the *trans* isomers. In the latter reduction, a rigid chair conformation of the six- and seven-membered rings forces the acetal functionality to point toward the β-face, thus interfering sterically with hydride transfer from this side. In this case, hydride transfer occurs from the α-face to give the β-alcohols.

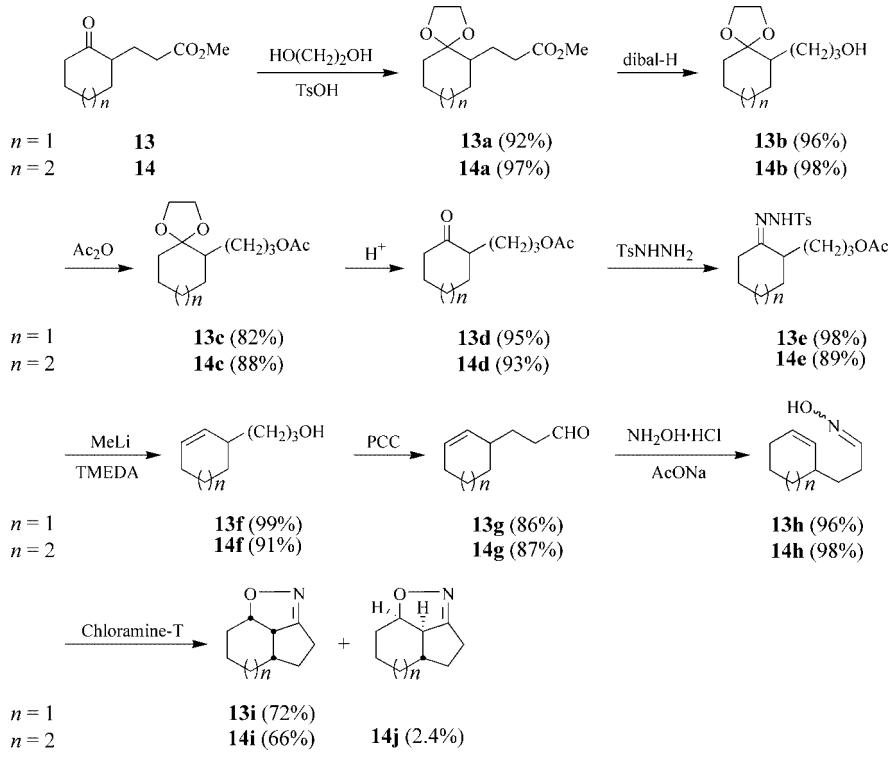
Mild hydrolysis of **9f**, **9g**, **11f**, and **11g** provided aldols **1a**, **2b**, **5a**, and **6b**. Isolation by column chromatography was refrained from in the cases of some of the product aldols, in order to circumvent the aforementioned epimerization and elimination obstacles. On attempted purification by chromatography on a silica gel column, ketones **9e** (*trans*) and **11d** (*cis*) were epimerized into **9d** (*cis*) and **11e** (*trans*), respectively. AM1 computations[15] indicated **9d** to be more stable than **9e** by 0.50 kcal mol^{-1} and **11e** to be more stable than **11d** by 2.73 kcal mol^{-1} (Table 1).

Even though the above synthetic steps were straightforward, hydrolysis of the acetalols proved problematic, the conditions having to be chosen very carefully so that deacetalization would proceed to completion without concomitant or subsequent dehydration to give the enones **9** or **11**. Recourse to aq. AcOH (25–50%)/THF or aq. HCl (0.5–2.5%)/THF (or MeOH) mixtures, stirring at room temp. or at reflux, and monitoring of the course of hydrolysis partly rectified this problem (see Exp. Sect.). Under more vigorous conditions (5–10% aq. HCl in THF; reflux 0.5–1 h) all aldols discussed here were dehydrated to enones **9** and **11**.

Table 1. Heats of formation (ΔH_f) of aldols, enones, and keto acetals as calculated by AM1, together with relative energies ($\Delta\Delta H_f$) of *cis*-fused vs. *trans*-fused isomers.[a]

Compd.	ΔH_f	$\Delta\Delta H_f$[b]	Compd.	ΔH_f	$\Delta\Delta H_f$
1a	–113.54	–1.32	**7a**	–116.09	2.98
2a	–112.22		**8a**	–119.07	
1b	–114.31	–2.40	**7b**	–119.63	–0.64
2b	–111.91		**8b**	–118.99	
5a	–118.83	1.52	**9**	–40.62	3.80
6a	–120.35		**10**	–44.42	
5b	–118.89	0.07	**11**	–46.19	4.87
6b	–118.95		**12**	–51.05	
3a	–115.26	–2.28	**9d**	–141.55	–0.50
4a	–112.98		**9e**	–141.05	
3b	–114.42	–3.38	**11d**	–145.46	2.73
4b	–111.04		**11e**	–148.19	

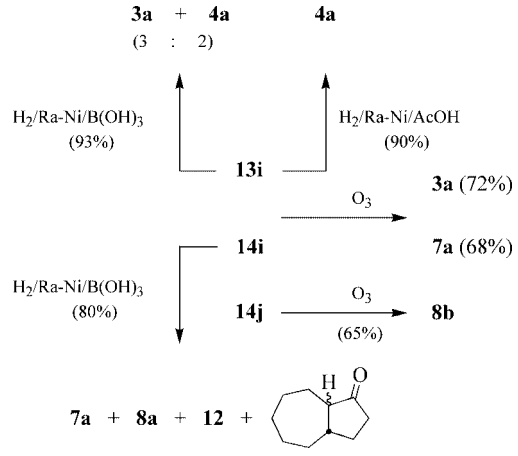
[a] Calculations were carried out on the most stable conformations. In **3a**, **4a**, **3b**, **8a**, and **7b**, OH was equatorial, and in **4b**, **7a**, and **8b** axial, according to ^{1}H NMR (see Table S1 in the Supporting Information). In aldols, the hydroxy hydrogen was *syn* to the carbonyl oxygen. [b] $\Delta\Delta H_f = \Delta H_f(cis) - \Delta H_f(trans)$ in kcal mol^{-1}. Negative differences indicate higher, and positive lower, stability of a compound relative to its isomer.



Scheme 2. Preparation of isoxazolines **13i**, **14i**, and **14j**.

We set out next to prepare the remaining eight ketols **3**, **4**, **7**, and **8**, with the carbonyl and hydroxy moieties interchanged on the two rings relative to the isomers **1**, **2**, **5**, and **6**. To this end we employed a well established isoxazoline method suitable for the synthesis of hydrindanone and hydroazulenone aldols[6j,16] in combination with a synthetic route similar to that presented in Scheme 1. The ready availability of keto esters **13** and **14** prompted us to use the sequence outlined in Scheme 2 for the preparation of the requisite isoxazolines. The last step involved ring-closure of the aldoximes with chloramine-T[17] to furnish the known *cis*-fused isoxazolines **13i** and **14i**, previously prepared by nitrocycloalkene routes.[16d] Interestingly, the *trans*-fused isoxazoline **14j** (see below for confirmation of stereochemistry) was also obtained in low yield, while no analogous *trans*-fused product was observed during cyclization of the six-membered homologue. Theoretically, the intramolecular 1,3-dipolar nitrile oxide cycloaddition may take place on either face of the double bond, while previous work on similar systems had shown a transition state giving rise to the *cis*-fused isoxazoline to be favored over that furnishing the *trans*-fused isomer.[6j,16c,18] Dreiding models also favored the *cis*-fused isoxazoline **13i** in this work, but the flexibility of the seven-membered ring (in relation to the six-membered) can overcome the relatively higher energetic barrier imposed in the transition state and thus provide a small amount of the *trans*-fused epimer **14j**.

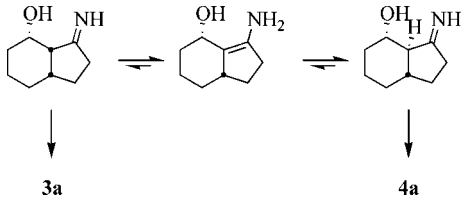
The isoxazolines **13i**, **14i**, and **14j** were unmasked under several sets of conditions described in the literature[6j,16,19] and illustrated in Scheme 3. Hydrogenolysis of **13i** with W-2 Ra-Ni/MeOH/H_2O/boric acid[19a] afforded **3a** and **4a**, whereas **14i** gave a more complex mixture consisting of the two epimeric aldols **7a** and **8a**, together with the enone **12** and an indeterminable quantity of *cis*- and *trans*-1-perhydroazulenones. Side products similar to these had also been found in a previous investigation.[6j] Further work using these conditions was abandoned.



Scheme 3. Unmasking of isoxazolines **13i**, **14i**, and **14j** to give aldols **3a**, **4a**, **7a**, and **8**.

Wollenberg[16d] had previously unmasked the isoxazoline **13i** to afford the aldol **3a** with H_2/W-2 Ra-Ni/MeOH/AcOH. When we repeated the exact experimental conditions reported, we mainly obtained the starting isoxazoline, but in other runs the use of a small excess of W-2 Ra-Ni furnished mixtures of both epimers **3a** and **4a**, their proportions varying with the quantity of catalyst used. With

use of even greater excesses of W-2 Ra-Ni (15- to 20-fold) we obtained **4a** exclusively (see Exp. Sect.); apparently, the imine–enamine tautomeric equilibrium,[16] shown in Scheme 4, was completely driven to the side of **4a**. Epimerization during hydrogenolysis of related decalin isoxazolines is on record.[18a]



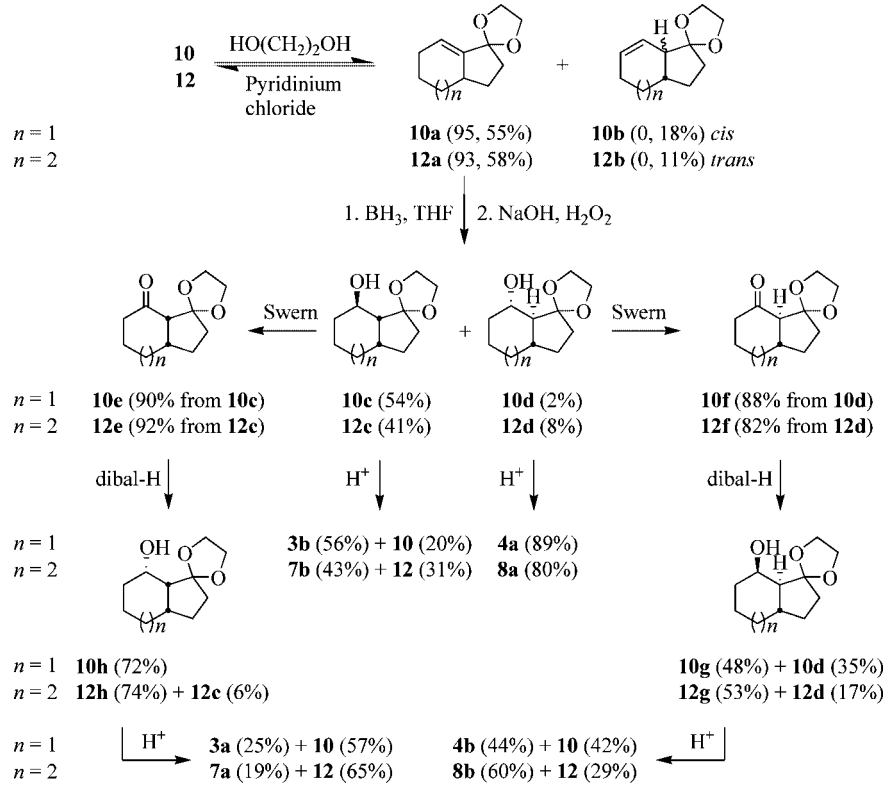
Scheme 4. Imine–enamine tautomeric equilibrium affording aldols **3a** and **4a**.

Unveiling the isoxazolines with O_3 (Scheme 3) proved to be a more stereoselective and reproducible process than hydrogenolysis for this type of isoxazolines. Ozonolysis[6j,16c,19b] of **13i** thus provided aldol **3a**, with spectral characteristics similar to those observed by Wollenberg, while isoxazolines **14i** and **14j** likewise gave the aldols **7a** and **8b**, respectively. We know of only one example of an aldol preparation by unmasking of a hydroazulenic isoxazoline.[6j] All the ozonolysis products were found to have retained the initial stereochemical integrity of the corresponding isoxazolines without any sign of epimerization, but passage of either **3a** or **4a** through a column filled with neutral silica gel would cause its partial epimerization to give an inseparable mixture of **3a/4a** ≈ 1:1. Under the same conditions, **7a** and **7b** were both completely epimerized to afford the seemingly more stable aldols **8a** and **8b**, respectively. Indeed, this is an efficacious alternative procedure for preparing **8a** and **8b**.

Our next efforts focused on the independent synthesis of **3a**, **4a**, **7a**, and **8b**, as well as on the synthesis of some aldols not obtained (or not obtained cleanly) by hydrogenolysis or ozonolysis (i.e., **3b**, **4b**, **7b**, **8a**) from enones **10**[9j,16d,20] and **12**, as illustrated in Scheme 5. Enones **10** and **12** thus furnished the ene acetals **10a** and **12a**, respectively, in high yield, although with use of excess catalyst the deconjugated isomers **10b** and **12b** were also obtained. A similar, but reversed, isomerization was also observed by Paquette.[20b]

Hydroboration/oxidation of **10a** and **12a** occurred mainly from the less hindered convex side as observed previously (Scheme 1), but with much higher diastereoselectivity, to furnish **10c** and **12c** as the major products alongside **10d** and **12d**. Mild oxidation to the ketones **10e**, **12e**, **10f**, and **12f** went smoothly, followed by dibal-H reduction to give the corresponding alcohols **10h**, **12h/12c**, **10g/10d**, and **12g/12d** in good yields. The high stereoselectivity of the previously observed reduction (Scheme 1) was seen here only in the cases of the *cis*-fused keto acetal **10e** and perhaps **12e**, but not for the *trans*-fused diastereomers **10f** and **12f**. Nevertheless, the reduction followed the same pattern as above; that is, hydride transfer took place predominantly from the less sterically congested side.

Mild deacetalization (vide supra) of the hydroxy acetals afforded the sought aldols. Most gratifyingly, preparation of authentic **8b** confirmed the assigned stereochemistry in



Scheme 5. Preparation of aldols **3**, **4**, **7**, and **8**.

isoxazoline **14j**, while the results were satisfactory for **4a** and **8a**. However, in other cases (**3**, **4b**, **7**, and **8b**) dehydration was unavoidable (see Exp. Sect.).

Further discussion on these undesirable eliminations is warranted. If the hydroxy group and its adjacent juncture hydrogen are *syn* to each other (*syn* elimination), the *cis*-fused aldols (**3b**, **7b**) are dehydrated more readily than the corresponding *trans*-fused epimers (**4a**, **8a**). Dreiding models indicate that dehydration in the *trans*-fused aldols, taking place from the α-side, appears to be more sterically blocked than in the *cis*-fused epimers, occurring from the β-side. If, on the other hand, the aforementioned configuration is *anti* (*anti* elimination), the energy of activation required to reach the transition state is smaller, and elimination here takes place to a greater extent for both the *cis*- (**3a**, **7a**) and the *trans*-fused (**4b**, **8b**) forms, although it is still predominant for the *cis*-fused epimers. Compared to the previous set of aldols (Scheme 1), elimination was not a problem except in the case of **5a** (*anti* elimination), where it occurred, although only to a small extent (10%). Even so, the yield of **5a** was still satisfactory (84%), and chromatographic isolation did not cause any epimerization.

The difference in the ease of dehydration between the two series of aldols may partly be sought in the thermodynamic stabilities of the product enones. A priori, it seems that the types **9** and **11** should be more strained than **10** and **12**, because the former compounds possess double bonds in their five-membered rings, the latter in their six- and seven-membered rings. Calculations,[15] shown in Table 1, confirmed this hypothesis. In relation to this, we note that some aldols are not dehydrated at all,[9a,9j,21] while others are only under vigorous conditions.[9a]

Theoretical computations[15] (Table 1) are consistent with previous findings indicating, in general, that *cis*-hydrindanone systems are more stable than *trans* but also that, inversely, *trans*-hydroazulenone carbocycles are more stable than the *cis* forms, with the **7b/8b** pair being an exception. The differences in the calculated stabilities, however, are not fully justifiable by the 100% completeness of the epimerizations observed in most cases (i.e., they are too small), suggesting some catalytic action provided by the silica gel acidic sites.

In conclusion, we have prepared sixteen diastereomerically pure aldols either by starting the synthesis from enones **9**, **10**, **11**, and **12** or by unmasking isoxazolines **13i**, **14i**, and **13j**.

Experimental Section

Representative procedures are given as examples. Columns used: A (85 × 2.5 cm, filled with 185 g of neutral Merck silica gel, 70–270 mesh), B (70 × 2.0 cm, 82 g), C (46 × 1.6 cm, 33 g), D (11 × 2.0 cm, 11 g). The columns were eluted with petroleum ether (b.p. 65–69 °C)/ethyl acetate *x*/*y* (v:v). Relative ratios of products, whenever pertinent, were determined by ^{1}H NMR integration. All compounds were obtained as colorless oils. Exceptions to the above are noted (see also Supporting Information).

1′,2′,5′,6′,7′,7a′-Hexahydrospiro[1,3-dioxolane-2,4′-indene] (9a): Enone **9** (6.94 g, 51.0 mmol),[9a,9j] ethylene glycol (15 mL), $TsOH·H_2O$ (250 mg, 1.31 mmol), and benzene (100 mL) were heated at reflux with continuous removal of water for 23 h. The mixture was worked up in the usual fashion (see Supporting Information) and purified on a column A (*x*/*y* = 20:1) to obtain **9a** (7.42 g, 81%). ^{1}H NMR: δ = 1.00 (qd, *J* = 11.9, *J* = 4.4 Hz, 1 H), 1.38–1.97 (m, 6 H), 2.14 (m, 1 H), 2.33 (m, 2 H), 2.71 (m, 1 H), 3.84 (m, 1 H), 3.91–4.09 (m, 3 H), 5.58 (m, 1 H) ppm. ^{13}C NMR: δ = 23.9, 30.5, 31.2, 34.9, 37.1, 45.0, 63.6, 65.3, 107.3, 122.9, 145.4 ppm. IR: $\tilde{\nu}$ = 3060, 2925, 1660, 1180, 1042, 932 cm^{-1}. MS (EI): *m*/*z* (%): 180 [M]$^+$ (10), 152 (58), 151 (12), 137 (35), 107 (17), 93 (34), 91 (40), 41 (100). $C_{11}H_{16}O_2$ (180.24) calcd: C 73.30, H 8.95; found C 72.95, H 8.79.

***rac*-(3′*S*,3a′*S*,7a′*S*)-Octahydrospiro[1,3-dioxolane-2,4′-inden]-3′-ol (9b) and *rac*-(3′*R*,3a′*R*,7a′*S*)-Octahydrospiro[1,3-dioxolane-2,4′-inden]-3′-ol (9c):** Ene acetal **9a** (6.43 g, 35.7 mmol) in anhydrous THF (50 mL) was hydroborated with BH_3·THF (1.0 M, 18.0 mL, 18.0 mmol) as described in the literature.[12] The mixture was stirred at room temp. for 1 h, quenched with water (3.0 mL), and warmed up to 50 °C, and NaOH (10%, 15 mL) was added, followed by the addition of H_2O_2 (35%, 12 mL). After stirring at room temp. for 1 h and the usual workup, the mixture was separated on a column A (*x*/*y* = 10:1, changed to *x*/*y* = 5:1 after 5 L had been eluted) to afford **9b** (first fraction, 3.02 g, 43%) and **9c** (second fraction, 1.43 g, 20%).

Compound 9b: Needles; m.p. 37–39 °C. ^{1}H NMR: δ = 0.97 (dddd, *J* = 13.0, *J* = 13.0, *J* = 13.0, *J* = 3.0 Hz, 1 H), 1.32–1.72 (m, 7 H), 1.82–2.02 (m, 2 H), 2.12–2.27 (m, 2 H), 2.90 (brs, OH), 3.98 (m, 4 H), 4.35 (ddd, *J* = 8.7, *J* = 8.7, *J* = 6.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 23.0, 28.70, 28.73, 30.6, 31.3, 38.8, 55.0, 64.3, 64.6, 73.7, 111.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3525, 2925, 1161, 1100, 1034, 920 cm^{-1}. MS (EI): *m*/*z* (%): 199 [M + 1]$^+$ (87), 198 [M]$^+$ (89), 181 (87), 155 (91), 137 (92), 126 (75), 115 (87), 99 (94), 94 (94), 86 (91), 42 (100). $C_{11}H_{18}O_3$ (198.26) calcd: C 66.64, H 9.15; found C 66.38, H 8.93.

Compound 9c: Off-white semisolid; m.p. 31–33 °C. ^{1}H NMR: δ = 1.02 (m, 1 H), 1.25–1.47 (m, 3 H), 1.48–1.64 (m, 3 H), 1.65–1.86 (m, 4 H), 2.04 (dddd, *J* = 13.6, *J* = 8.7, *J* = 8.7, *J* = 8.7 Hz, 1 H), 2.27 (brs, OH), 4.01 (m, 4 H), 4.22 (ddd, *J* = 8.6, *J* = 8.6, *J* = 5.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 24.1, 29.2, 31.1, 31.5, 34.8, 41.1, 59.0, 64.2, 65.2, 71.7, 110.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3555, 2920, 1143, 1102, 1040, 941 cm^{-1}. MS (EI): *m*/*z* (%): 198 [M]$^+$ (89), 181 (59), 155 (97), 137 (81), 126 (56), 115 (97), 99 (96), 94 (46), 86 (82), 41 (100). $C_{11}H_{18}O_3$ (198.26) calcd: C 66.64, H 9.15; found C 66.43, H 9.20.

***rac*-(3*S*,3a*S*,7a*S*)-3-Hydroxyoctahydro-4*H*-inden-4-one (1b):** Acetalol **9b** (83 mg, 0.419 mmol), aq. AcOH (50%, 2 mL), and THF (2 mL) were heated at reflux for 20 min. Purification on a column C (*x*/*y* = 5:1) gave aldol **1b** (61 mg, 94%). ^{1}H NMR: δ = 1.20–1.46 (m, 2 H), 1.53 (m, 1 H), 1.68–1.95 (m, 4 H), 2.07 (m, 1 H), 2.22–2.40 (m, 2 H), 2.50 (dd, *J* = 5.8, *J* = 5.5 Hz, 1 H), 2.65 (m, 1 H), 2.79 (brs, OH), 4.50 (q, *J* = 6.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 23.1, 28.5, 28.9, 33.3, 40.05, 40.14, 60.8, 74.6, 214.3 ppm. IR: $\tilde{\nu}$ = 3418, 2938, 1703, 1461, 1350, 1053, 1018 cm^{-1}. MS (EI): *m*/*z* (%): 154 [M]$^+$ (3), 136 (39), 110 (72), 107 (51), 97 (83), 94 (90), 83 (48), 80 (96), 41 (100). $C_9H_{14}O_2$ (154.21) calcd: C 70.10, H 9.15; found C 70.27, H 9.38.

***rac*-(3a′*S*,7a′*S*)-Hexahydrospiro[1,3-dioxolane-2,4′-inden]-3′(3a′*H*)-one (9d):** A mixture of pyridinium chlorochromate (PCC),[14] (3.51 g, 16.3 mmol) and CH_2Cl_2 (60 mL) was stirred at room temp. for 15 min and a solution of the hydroxy acetal **9b** (2.18 g, 11.0 mmol) in CH_2Cl_2 (5 mL) was added all at once. The mixture was further stirred at room temp. for 24 h and chromatographed

directly (no workup) on a column B (*x*/*y* = 5:1) to afford acetalone **9d**, (2.10 g, 97%). ^{1}H NMR: δ = 1.32–1.54 (m, 2 H), 1.54–1.79 (m, 4 H), 1.79–1.94 (m, 1 H), 2.00 (m, 1 H), 2.11–2.39 (m, 2 H), 2.45 (d, *J* = 7.4 Hz, 1 H), 2.52 (m, 1 H), 3.85–3.97 (m, 4 H) ppm. 2D ^{1}H–^{1}H COSY. ^{13}C NMR: δ = 20.0, 25.2, 26.4, 33.7, 37.3, 37.6, 55.8, 63.9, 65.3, 109.0, 217.4 ppm. 2D ^{1}H–^{13}C COSY. IR: $\tilde{\nu}$ = 2941, 1745, 1156, 1110, 1035, 950 cm^{-1}. MS (EI): *m*/*z* (%): 196 [M]$^+$ (15), 153 (23), 113 (13), 99 (100), 86 (61). $C_{11}H_{16}O_3$ (196.24) calcd: C 67.32, H 8.22; found C 67.26, H 8.24.

***rac*-(3a′*R*,7a′*S*)-Hexahydrospiro[1,3-dioxolane-2,4′-inden]-3′(3a′*H*)-one (9e):** Acetalol **9c** (806 mg, 4.07 mmol) was oxidized by the method described by Swern and associates[13] (30 min at –78 °C), to provide acetalone **9e** (773 mg, 97%). White solid; m.p. 83–84 °C. ^{1}H NMR: δ = 1.16 (m, 1 H), 1.34–1.63 (m, 3 H), 1.69–2.15 with d, *J* = 13.7 Hz at δ = 1.88 (m, 7 H), 2.29 (m, 1 H), 3.87 (m, 1 H), 4.01 (m, 2 H), 4.29 (m, 1 H) ppm. ^{13}C NMR: δ = 24.0, 27.2, 31.5, 37.0, 38.0, 41.6, 60.6, 65.4, 65.7, 108.4, 213.8 ppm. 2D ^{1}H–^{13}C COSY (mixture of **9e** + **9d**). IR (KBr): $\tilde{\nu}$ = 2938, 2888, 1739, 1448, 1359, 1342, 1212, 1179, 1151, 1106, 1053, 1041, 960, 911 cm^{-1}. MS (EI): *m*/*z* (%): 196 [M]$^+$ (16), 153 (100), 133 (9), 113 (13), 109 (22), 99 (21). $C_{11}H_{16}O_3$ (196.24) calcd: C 67.32, H 8.22; found C 67.46, H 8.30.

***rac*-(3′*R*,3a′*S*,7a′*S*)-Octahydrospiro[1,3-dioxolane-2,4′-inden]-3′-ol (9f):** A dibal-H solution (1.0 M in CH_2Cl_2, 18.0 mL, 18.0 mmol) was added slowly by syringe, at –78 °C under anhydrous conditions, to a solution of the keto acetal **9d** (1.75 g, 8.92 mmol) in CH_2Cl_2 (90 mL). The mixture was stirred for 1 h, allowed to warm to 0 °C over 2 h, quenched with water (5 mL), and worked up to furnish the hydroxy acetal **9f** diastereoselectively. Purification on a column C (*x*/*y* = 5:1) afforded 1.43 g (81%). ^{1}H NMR: δ = 1.30–1.86 (m, 9 H), 1.94 (t, *J* = 6.9 Hz, 1 H), 2.09 (m, 2 H), 2.42 (d, *J* = 2.1 Hz, OH), 3.99 (m, 4 H), 4.40 (m, 1 H) ppm. ^{13}C NMR: δ = 22.8, 28.5, 30.5, 32.8, 34.6, 39.0, 51.9, 63.9, 64.5, 73.6, 110.8 ppm. IR: $\tilde{\nu}$ = 3486, 2935, 1109, 1074, 1044, 1020, 930 cm^{-1}. MS (EI): *m*/*z* (%): 198 [M]$^+$ (35), 181 (17), 155 (93), 141 (41), 136 (58), 126 (48), 115 (99), 100 (89), 99 (95), 86 (96), 55 (100). $C_{11}H_{18}O_3$ (198.26) calcd: C 66.64, H 9.15; found C 66.48, H 9.39.

3-(2-{2-[(4-Methylphenyl)sulfonyl]hydrazono}cyclohexyl)propyl Acetate (13e): Keto acetate **13d** (2.48 g, 12.5 mmol), 4-methylbenzenesulfonohydrazide (2.39 g, 12.8 mmol), and methanol (30 mL) were heated at reflux for 4 h. The mixture was cooled and the solid *p*-tosylhydrazone derivative **13e** was isolated by filtration. The mother liquor was concentrated and cooled, and a second crop was isolated (total of 4.48 g, 98%). Recrystallization from EtOH gave **13e** as white leaflets; m.p. 123–124 °C. ^{1}H NMR: δ = 1.20–2.50 (m, 19 H) with s at δ = 2.05 and 2.40 ppm, 3.94 (t, *J* = 6.4 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.74 (br s, NH), 7.84 (d, *J* = 8.2 Hz, 2 H) ppm. ^{13}C NMR: δ = 21.0, 21.6, 23.8, 25.9, 26.1, 26.2, 27.4, 33.2, 43.8, 64.6, 128.3, 129.4, 135.4, 143.9, 163.5, 171.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3280, 3195, 3015, 2920, 1715, 1590, 1440, 1377, 1360, 1323, 1243, 1158, 1087, 1030, 1012 cm^{-1}. $C_{18}H_{26}N_2O_4S$ (366.47) calcd: C 58.99, H 7.15, N 7.64; found C 59.06, H 7.15, N 7.78.

3-Cyclohex-2-en-1-ylpropan-1-ol (13f):[22] As described in a previously published procedure,[9a] *p*-tosylhydrazone **13e** (4.25 g, 11.6 mmol), MeLi (1.6 M in ether, 50 mL, 80 mmol), and TMEDA (20 mL) in dry THF (120 mL) afforded, after 23 h at room temp., the known[22] alkenol **13f**, which was purified on a column B (*x*/*y* = 10:1), to give 1.61 g (99%). ^{1}H NMR: δ = 1.16–1.86 (m, 9 H), 1.93–2.14 (m, 3 H), 3.64 (t, *J* = 6.6 Hz, 2 H), 5.57 (m, 1 H), 5.67 (m, 1 H) ppm. ^{13}C NMR: δ = 21.5, 25.4, 29.1, 30.2, 32.4, 35.0, 63.3, 127.1, 131.8 ppm. IR: $\tilde{\nu}$ = 3374, 3016, 2929, 1648, 1449, 1376, 1250, 1057, 1031 cm^{-1}.

(1*E*)- and (1*Z*)-3-Cyclohex-2-en-1-ylpropanal Oxime (13h): As described in a published procedure,[23] enal **13g** (3.51 g, 25.4 mmol), hydroxylamine hydrochloride (1.93 g, 27.8 mmol), sodium acetate trihydrate (4.11 g, 30.2 mmol), water (40 mL), and acetonitrile (120 mL) were stirred at room temp. for 23 h to afford a ca. 1.1:1 mixture of (*E*)/(*Z*) isomers of **13h** (3.73 g, 96%). ^{1}H NMR: δ = 1.13–2.16 (m, 19 H), 2.26 (m, 2 H), 2.44 (td, *J* = 7.9, *J* = 5.5 Hz, 2 H), 5.56 (m, 2 H), 5.69 (m, 2 H), 6.73 [t, *J* = 5.5 Hz, 1 H, (*Z*)–CH=N], 7.44 [t, *J* = 6.1 Hz, 1 H, (*E*)–CH=N], 8.49 (br s 1 H, OH) ppm. ^{13}C NMR: δ = 21.34, 21.36, 22.6, 25.3 (2 C), 27.0, 28.7 (2 C), 32.4, 32.9, 34.6, 34.9, 127.6 (2 C), 131.05, 131.10, 152.3, 152.9 ppm. IR: $\tilde{\nu}$ = 3260, 3108, 3017, 2925, 1648, 1450, 1431, 1314, 1285, 931 cm^{-1}. MS (EI): *m*/*z* (%): 154 [M + 1]$^+$ (81), 153 [M]$^+$ (67), 136 (71), 134 (87), 121 (80), 119 (62), 117 (50), 108 (88), 96 (78), 92 (100), 91 (70). $C_9H_{15}NO$ (153.22) calcd: C 70.55, H 9.87, N 9.14; found C 70.76, H 9.99, N 9.11.

***rac*-(4a*S*,7a*S*,7b*S*)-3,4,4a,5,6,7,7a,7b-Octahydroindeno[1,7-*cd*]-isoxazole (13i):**[16d] As described in an established procedure,[17] aldoxime **13h** (3.58 g, 23.4 mmol), chloramine-T trihydrate[24] (7.24 g, 25.7 mmol), and EtOH (450 mL) were heated at reflux for 12 h. Purification on a column A (*x*/*y* = 10:1, changed to *x*/*y* = 5:1 after 2 L had been eluted), gave the known[16d] isoxazoline **13i** (2.55 g, 72%). ^{1}H NMR:[25] δ = 0.86–1.05 (m, 2 H), 1.28 (m, 1 H), 1.52 (m, 1 H), 1.72 (m, 1 H), 1.92–2.11 (m, 2 H), 2.25 (m, 1 H), 2.32–2.52 (m, 3 H), 3.64 (td, *J* = 8.5, *J* = 1.0 Hz, 1 H), 4.68 (td, *J* = 8.7, *J* = 8.4 Hz, 1 H) ppm. 2D ^{1}H–^{1}H COSY. ^{13}C NMR:[25] δ = 19.2, 20.4, 27.9, 28.9, 34.2, 36.1, 57.5, 78.4, 172.6 ppm. 2D ^{1}H–^{13}C COSY. $C_9H_{13}NO$ (151.21) calcd: C 71.49, H 8.67, N 9.26; found C 71.26, H 8.93, N 9.11.

***rac*-(4a*S*,8a*S*,8b*S*)-4,4a,5,6,7,8,8a,8b-Octahydro-3*H*-azuleno[1,8-*cd*]isoxazole (14i)[16] and *rac*-(4a*S*,8a*R*,8b*R*)-4,4a,5,6,7,8,8a,8b-Octahydro-3*H*-azuleno[1,8-*cd*]isoxazole (14j):** These compounds were prepared from aldoxime **14h** (3.26 g, 19.5 mmol), chloramine-T trihydrate[24] (6.23 g, 22.1 mmol), and EtOH (390 mL) as described above. Separation on a column A (*x*/*y* = 10:1) afforded the known[16] isoxazoline **14i** (2.12 g, 66%) and **14j** (77 mg, 2.4%).

Compound 14i: ^{1}H NMR: δ = 1.12–2.54 (m, 13 H), 3.81 (dd, *J* = 11.4, *J* = 6.8 Hz, 1 H), 4.73 (ddd, *J* = 11.5, *J* = 6.8, *J* = 2.4 Hz, 1 H) ppm. 2D ^{1}H–^{1}H COSY. ^{13}C NMR: δ = 20.1, 23.1, 28.4, 31.0, 31.7, 35.3, 39.3, 61.3, 81.8, 167.6 ppm. 2D ^{1}H–^{13}C COSY. $C_{10}H_{15}NO$ (165.23) calcd: C 72.69, H 9.15, N 8.48; found C 72.41, H 9.38, N 8.29.

Compound 14j: ^{1}H NMR: δ = 1.07–1.48 (m, 3 H), 1.55–1.94 (m, 6 H), 2.01–2.23 (m, 2 H), 2.41–2.49 (m, 2 H), 3.35 (t, *J* = 11.1 Hz, 1 H), 4.67 (td, *J* = 11.1, *J* = 5.8 Hz, 1 H) ppm. 2D ^{1}H–^{1}H COSY. ^{13}C NMR: δ = 20.9, 24.7, 30.7, 32.0, 32.5, 33.6, 41.5, 65.3, 81.5, 167.2 ppm. 2D ^{1}H–^{13}C COSY. IR: $\tilde{\nu}$ = 1595, 1567, 1469, 1371, 1260, 1220, 1119, 1096, 980, 908 cm^{-1}. $C_{10}H_{15}NO$ (165.23) calcd: C 72.69, H 9.15, N 8.48; found C 72.95, H 9.01, N 8.53.

***rac*-(3a*S*,7*S*,7a*R*)-7-Hydroxyoctahydro-1*H*-inden-1-one (3a) and *rac*-(3a*S*,7*S*,7a*S*)-7-Hydroxyoctahydro-1*H*-inden-1-one (4a)**

A) By Hydrogenolysis of Isoxazoline 13i in the Presence of W-2 Ra-Ni/B(OH)$_3$: As described in a literature procedure,[19a] isoxazoline **13i** (271 mg, 1.79 mmol), boric acid (227 mg, 3.67 mmol), a spatula tip of W-2 Ra-Ni (ca. 15–20 mg), and MeOH/H_2O 5:1 (10 mL) were stirred under hydrogen for 5 h to furnish a mixture of aldols **3a** and **4a** (ca. 3:2, 257 mg, 93%). Use of a column B (*x*/*y* = 10:1) failed on one hand to separate the mixture, while on the other hand it caused some epimerization (**3a**/**4a** ≈ 1:1). The mixture of **3a** and **4a** obtained above gave enone **10**[9j,16d,20] (63%) upon treatment with methanesulfonyl chloride and 1,5-diazabicyclo[5.4.0]undec-5-

ene (DBU), as described in the literature.[16d] The same result was obtained after **3a/4a** had been heated at reflux in aq. HCl (5%, 3.0 mL) and THF (5.0 mL) for 15 min (82% yield). In fact, all of the hydrindene aldols presented in this paper were dehydrated to **10** under the latter conditions, with yields ranging from 75 to 95%, after purification by column chromatography.

B) By Hydrogenolysis of Isoxazoline 13i in the Presence of W-2 Ra-Ni/AcOH: Under conditions and with reagents identical to those described by Wollenberg[16d] (except that 1.0 mL of MeOH was used, instead of 0.5 mL), we obtained mainly starting material. In a second run, addition of ca. 5 mg of W-2 Ra-Ni (instead of ca. 1 mg) while keeping all other conditions constant, furnished a mixture of both **3a** and **4a** (88%), with predominance of the latter (>70%). In a third run, in which the quantity of W-2 Ra-Ni was further increased to ca. 15–20 mg, nearly pure **4a** (>95%) was obtained in 90% yield. Column chromatography of pure **4a** (column B, *x*/*y* = 10:1) resulted in an epimeric mixture **3a/4a** ≈ 1:1.

C) By Ozonolysis of Isoxazoline 13i: As described in a literature procedure,[19b] isoxazoline **13i** (137 mg, 0.906 mmol), in CH_2Cl_2/MeOH (5:1, 25 mL), was subjected to a stream of O_3/O_2 for 3 h at –78 °C, stirred for an additional 3 h, and quenched with dimethyl sulfide. Workup gave pure **3a** (101 mg, 72%). Column chromatography, however (column B, *x*/*y* = 10:1), resulted in an epimeric mixture **3a/4a** ≈ 1:1.

D) By Deacetalization of β-Hydroxy Acetal 10h: A solution of **10h** (71 mg, 0.358 mmol), aq. AcOH (25%, 3.0 mL), and THF (5.0 mL) was treated as described in the representative procedure (5.0 min at reflux) to afford a mixture of **10h/10/3a** ≈ 1:6:3 (43 mg). Estimated yields (based on converted starting material): **10** (26 mg, 57%), **3a** (13 mg, 25%).

E) By Deacetalization of β-Hydroxy Acetal 10d: A solution of **10d** (39 mg, 0.197 mmol), aq. HCl (2.5%, 1.0 mL), and MeOH (5.0 mL) was stirred at room temp. for 10 h to provide **4a** (27 mg, 89%).

Compound 3a: Data similar to those described in the literature,[16d] with an additional signal in the ^{13}C NMR at δ = 37.6 ppm, missing in the original paper. 2D ^1H–^1H COSY (mixture of **3a** + **4a**). 2D ^1H–^{13}C COSY (mixture of **3a** + **4a**).

Compound 4a: ^1H NMR: δ = 1.08–1.38 (m, 3 H), 1.48–1.68 (m, 3 H), 1.68–2.19 (m, 5 H), 2.22–2.53 (m, 1 H), 3.50 (s, 1 H, OH), 3.75 (ddd, *J* = 9.9, *J* = 9.2, *J* = 4.6 Hz, 1 H) ppm. 2D ^1H–^1H COSY (mixture of **4a** + **3a**). ^{13}C NMR: δ = 24.6, 27.3, 31.5, 33.9, 37.3, 41.2, 61.0, 70.3, 220.1 ppm. 2D ^1H–^{13}C COSY (mixture of **4a** + **3a**). IR: $\tilde{\nu}$ = 3482, 2915, 1718, 1397, 1164, 1066, 1051, 1007 cm^{-1}. $C_9H_{14}O_2$ (154.21) calcd: C 70.10, H 9.15; found C 69.96, H 8.91.

Supporting Information (see also the footnote on the first page of this article): Most of the Experimental Section. Two-dimensional (2D) ^1H–^1H COSY and 2D ^1H–^{13}C COSY spectra.

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[24] Sodium chloro[(4-methylphenyl)sulfonyl]azanide.

[25] There are some differences between our NMR spectra and those reported.[16d]

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