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Tandem Single-Step Construction of Chiral Hexahydrophenanthrenes: A Concise Route to (+)-Ferruginol

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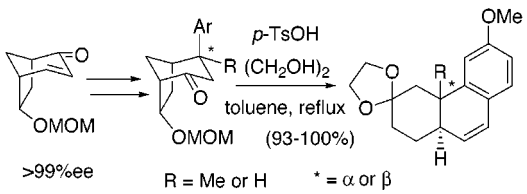
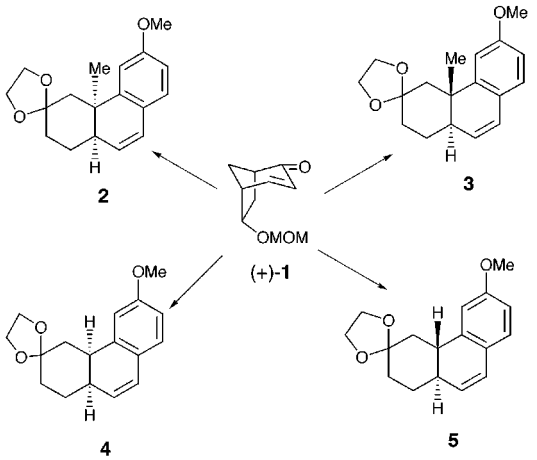
ABSTRACT



An efficient enantio- and diastereocontrolled construction of hydrophenanthrenes having either a quaternary or a tertiary benzylic stereogenic center has been developed by employing a tandem retro-aldol and intramolecular Friedel–Crafts alkylation sequence. Its application to a diastereocontrolled synthesis of an abietane diterpenoid (+)-ferruginol has also been demonstrated.

A hydrophenanthrene framework is the backbone of a number of natural products such as certain diterpenoids[1] and morphine-type alkaloids.[2] Development of an efficient procedure for enantio- and diastereocontrolled construction of hydrophenanthrenes is, therefore, very important as a limited number of methods, in particular, enantio- and diastereocontrolled methods, have been established so far.[3] We report here an efficient convergent route to the A-ring saturated hexahydrophenathrenes **2**−**5** having either a quaternary or a tertiary benzylic stereogenic center made diastereoselectively in enantiopure forms. The route starts from a common chiral building block, **1**, having a bicyclo[3.2.1]octenone framework, which could be prepared in both enantiomeric forms from racemic norbornane-2,5-dione[4] and in enantiopure forms by employing lipase-mediated kinetic resolution.[5] The key reaction involves an acid-catalyzed tandem retro-aldol cleavage and an aldol-type cyclization sequence which proceeds in one step in a very facile manner without losing the original stereochemical integrity generated on the basis of the inherent stereochemical nature of the chiral building block **1** (Scheme 1).

Scheme 1



The chiral building block **1** was prepared in both enantiomerically pure forms from recemic bicyclic diketone[4]

(1) (a) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*, Vol. II; Academic Press: New York, 1972; p 185. (b) Hanson, J. R. *Nat. Prod. Rep.* **2000**, *17*, 165 and previous reports.

(2) (a) Kametani, T. *The Chemistry of the Isoquinoline Alkaloids*, Vol. 2, Chapter 10; Kinkodo: Sendai, 1974. (b) Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148 and previous reports.

(3) (a) Floyd, A. J.; Dyke, S. F.; Wards, S. E. *Chem. Rev.* **1976**, *76*, 509. (b) Sutherland, J. K. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M., Fleming, I., Ed.; Pergamon: Oxford, 1991; p 341.

(4) Hawkins, R. T.; Hsu, R. S.; Wood, S. G. *J. Org. Chem.* **1978**, *43*, 4648.

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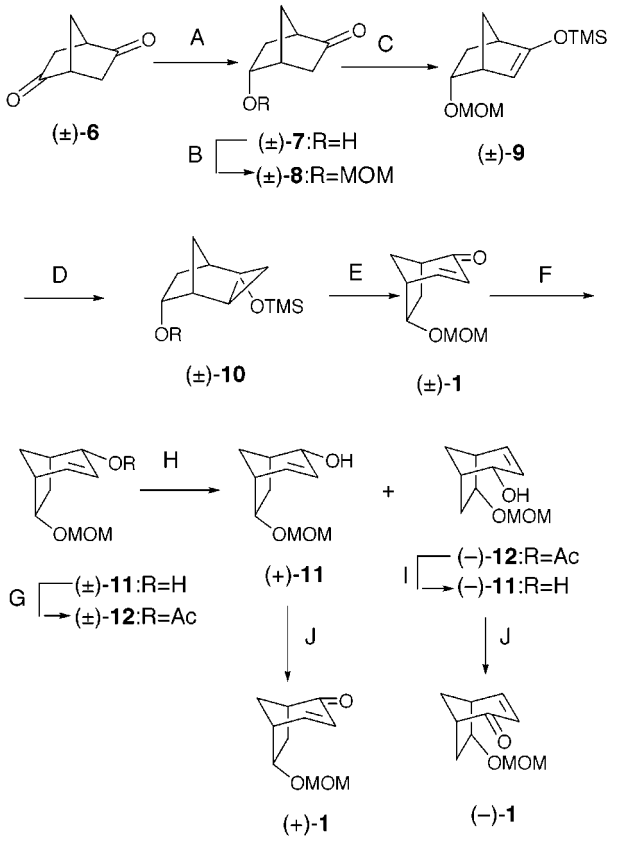
(±)-**6** by employing lipase-mediated resolution. Thus, (±)-**6** was first transformed into racemic enone (±)-**1** in five steps of reactions involving controlled reduction and oxidative ring-expansion.[6] Although the endo-alcohol (±)-**11** generated diastereoselectively from (±)-**1** could not be resolved satisfactorily, the acetate (±)-**12** therefrom was resolved in clear-cut manner under hydrolysis conditions in the presence of Lipase PS to give enantiopure alcohol[7a] (+)-**11**, $[\alpha]^{27}_D$ +143.7 (*c* 1.0, $CHCl_3$), leaving enantiopure acetate (−)-**12**, $[\alpha]^{23}_D$ −106.5 (*c* 1.0, $CHCl_3$). Enantiopure enone (+)-**1**,[7b] $[\alpha]^{27}_D$ +433.2 (*c* 1.1, $CHCl_3$)], was obtained from the former by oxidation, and the enantiomer (−)-**1**,[7b] $[\alpha]^{25}_D$ −438.6 (*c* 1.6, $CHCl_3$), was obtained from the latter by sequential alkaline methanolysis and oxidation of the resulting alcohol[7a] (−)-**11**, $[\alpha]^{25}_D$ −142.3 (*c* 1.0, $CHCl_3$), both in satisfactory yields (Scheme 2).

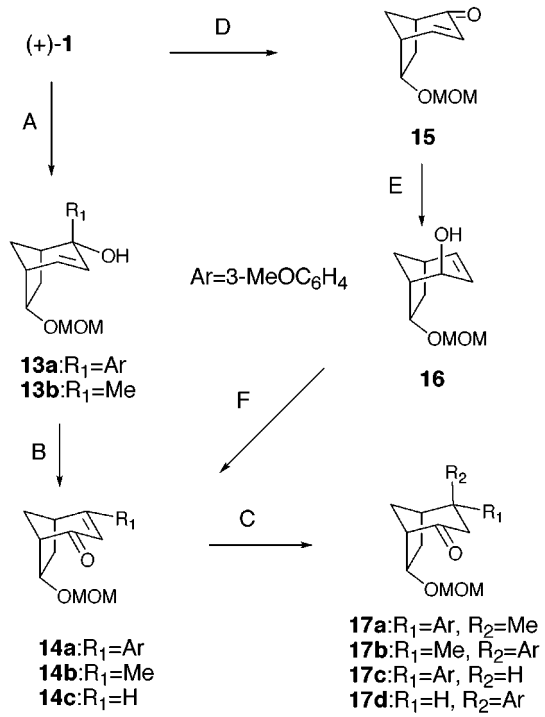
Scheme 2[a]



[a] Reagents and conditions: (A) LiAl(O-*t*-Bu)$_3$H, THF; (B) MOM-Cl, Hünig base, CH_2Cl_2 (95%, two steps); (C) LDA, TMS-Cl, THF; (D) Et_2Zn, CH_2I_2, CH_2Cl_2 (80%, two steps); (E) $FeCl_3$, DMF then DBU (86%); (F) DIBAL, CH_2Cl_2 (91%); (G) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2 (98%); (H) Lipase PS, 0.1 N phosphate buffer−acetone (10:1), 25 d (44%:>99% ee for (+)-**11** and 44%: >99%ee for (−)-**12**); (I) K_2CO_3, MeOH (99%); (J) MnO_2, CH_2Cl_2 (96% for (+)-**1** and 97% for (−)-**1**).

Four key intermediates **17a**−**d** were prepared from (+)-**1** in a diastereocontrolled manner as shown in Scheme 3.

Scheme 3[a]



[a] Reagents and conditions: (A) for **13a** ArBr, *n*-BuLi, THF (95%); for **13b** MeLi, THF (97%); (B) PCC, CH_2Cl_2 (59% for **14a**; 91% for **14b**); (C) for **17a** Me_2CuLi, THF (74%); for **17b** ArMgBr, CuI, THF (92%); for **17c** (from **14a**) DIBAL, CuI, THF (93%); for **17d** (from **14c**) ArMgBr, CuI, THF (73%); (D) 30% H_2O_2, 10% NaOH−THF (92%); (E) NH_2NH_2−HCl, Et_3N, MeCN (69%); (F) MnO_2, CH_2Cl_2 (91%).

Owing to its molecular bias, (+)-**1** allowed diastereospecific introduction of a nucleophile from the convex face of the molecule to introduce either a quaternary or a tertiary stereogenic center through a 1,4-addition reaction on the enone functionality. Thus, the two diastereomeric ketones **17a** and **17b**, each containing a quaternary benzylic stereogenic center, were prepared diastereoselectively by just altering the order of the 1,2- and 1,4-addition sequence. On the other hand, one of two diastereomeric tertiary benzylic ketones **17c** having an *endo*-aryl group was prepared through a convex face selective hydrogenation of the *β*-aryl enone **14a**. The other diastereomer **17d** having an *exo*-aryl group was prepared by a convex face selective 1,4-addition of the aryl functionality to the enone **14c** obtained from the same chiral building block (+)-**1** through a three-step 1,3-ketone transposition sequence via **15** and **16** involving the Wharton rearrangement[8] (Scheme 3).

Since facile retro-aldol cleavage was reported for bicyclo-[2.2.2]octane derivatives having a *β*-alkoxy ketone func-

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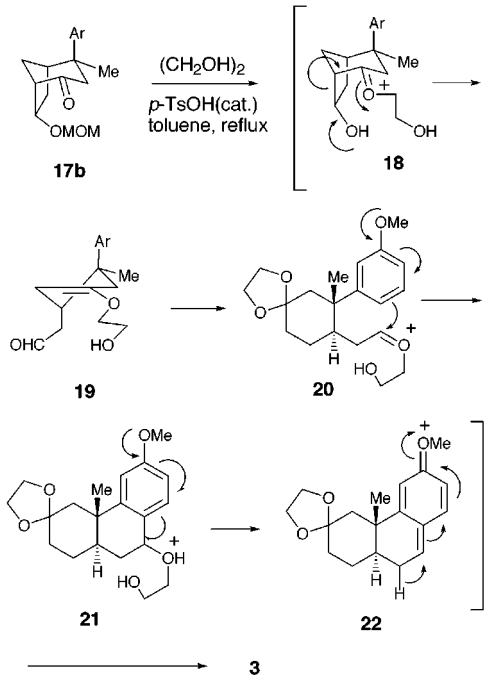
(6) Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. VI, p 327.

(7) (a) Optical purities of the alcohol **11** were determined by ^{1}H NMR spectra after transformation into the (*R*)- and (*S*)-MTPA esters. (b) Optical purities of the enone **1** were determined by HPLC using a chiral column (CHIRALCEL OD, elution with ^{i}PrOH−hexane 1:99 v/v).

(8) Caine, D. *Org. Prep. Proc. Int.* **1988**, *20*, 1.

tionality,[9] and since we have recently developed facile hydrophenanthrene formation in a certain γ-arylbutanal derivative under acetalization conditions,[10] we treated **17b** with ethylene glycol in toluene at reflux temperature in the presence of a catalytic amount of *p*-toluenesulfonic acid in expectation of obtaining a hydrophenanthrene product. A facile and clean reaction took place to give a single product in quantitative yield, and it was, gratifyingly, found to be the A-ring saturated A/B-*trans*-hexahydrophenanthrene **3** having a quaternary benzylic stereogenic center (Scheme 4)

Scheme 4



Under the same conditions, the diastereomer **17a** furnished diastereoselectively the corresponding A/B-*cis*-hexahydrophenanthrene **2** in excellent yield. Similarly, the two diastereomers **17c** and **17d**, each having a tertiary benzylic stereogenic center, furnished the corresponding A-ring saturated hydrophenanthrenes A/B-*cis*-**4** and A/B-*trans*-**5**, diastereoselectively, in excellent yields (Table 1).

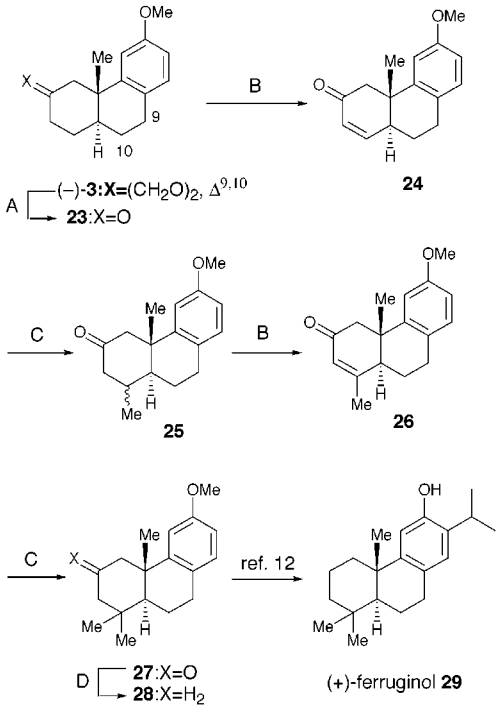
Table 1. Yields of the Hydrophenanthrenes **2**−**5** from the Ketones **17a**−**d**

entry	ketone	time (h)	product	yield (%)
1	**17a**	4	**2**	98
2	**17b**	3	**3**	100
3	**17c**	1.5	**4**	93
4	**17d**	1.5	**5**	94

Although we did not carry out a detailed examination, it is apparent that the presence of ethylene glycol is essential to attain excellent yields as the reaction proceeded very slowly and was accompanied by a mixture of byproducts when ethylene glycol was absent. This indicated that the reaction, as exemplified by **17b**, commenced with concomitant ethylene glycol-mediated cleavage of the MOM ether and ketalization of the ketone functionality leading to the activated intermediate **18** which then collapsed to the aldehyde **19** by a retro-aldol reaction. Owing to the ethylene glycol present, the reaction proceeded further to generate the next activated intermediate **20** which underwent an intramolecular Friedel−Crafts alkylation to give the final hexahydrophenanthrene **3** via the intermediates **21** and **22**. During the tandem process the original stereochemical integrity of the starting materials remained intact (Scheme 4).

To confirm the stereochemistry of the four A-ring hexahydrophenanthrenes **2**−**5** thus obtained, the *trans*-AB diastereomer **3** having a quaternary benzylic stereogenic center was transformed into the known compound[11] **28** serving as the key intermediate of an enantioselective synthesis of the abietane diterpenoid (+)-ferruginol **29** isolated from *Salvia* species.[12] Thus, on sequential deketalization and catalytic hydrogenation, (−)-**3**, mp 67−69 °C, $[\alpha]^{25}_D$ −145.6 (*c* 1.0, $CHCl_3$), obtained from (+)-**1** (>99% ee), gave the ketone **23**, mp 96−98 °C, $[\alpha]^{25}_D$ +70.4 (*c* 1.0, $CHCl_3$). Reaction of **23** with 2-iodoxybenzoic acid (IBX) in the presence of *p*-toluenesulfonic acid in toluene containing DMSO[13] furnished the α,β-unsaturated ketone **24**, mp 66−68 °C, $[\alpha]^{26}_D$

Scheme 5[a]



[a] Reagents and conditions: (A) *p*-TsOH, acetone−H_2O (9:1) then H_2, 10% Pd/C, AcOEt (100%); (B) iodoxybenzoic acid (IBX), *p*-TsOH, toluene−DMSO (96% for **24** and 56% for **26**); (C) Me_2CuLi, Et_2O (93% for **25** and 92% for **27**); (D) NH_2NH_2−H_2O, KOH, triethylene glycol, ∼200 °C (81%).

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(10) Yamada, O.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2785.

−150.5 (*c* 1.0, $CHCl_3$), which on 1,4-addition gave the *β*-methyl ketone **25** as a 4:1 diastereomeric mixture. Iterative treatment of the mixture of ketone **25** with IBX under the same conditions as above afforded the single *β*-methyl enone **26**, mp 118−120 °C, $[\alpha]^{27}_D$ +129.9 (*c* 1.0, $CHCl_3$)], which on 1,4-addition gave the *β*,*β*-dimethyl ketone **27**, mp 109−112 °C, $[\alpha]^{25}_D$ +42.8 (*c* 0.9, $CHCl_3$). Finally, **27** was reduced under Wolff−Kishner conditions[14] to give the known hydrocarbon[11] **28**, $[\alpha]^{23}_D$ +64.4 (*c* 1.0, $CHCl_3$) {lit.[11] $[\alpha]_D$ +64.0 (*c* 1.0, $CHCl_3$)}, to complete a formal synthesis of (+)-ferruginol **29**. This has confirmed the structure of **17b** as well as those of **17a**, **17c**, and **17d** (Scheme 5).

In conclusion, we have developed an enantio- and diastereocontrolled route to the A-ring saturated *cis*- and *trans*-AB-hexahydrophenanthrenes carrying either a quaternary or a tertiary benzylic stereogenic center starting from a common chiral building block having a bicyclo[3.2.1]octenone framework. Since the chiral building block used in the present study allows diastereocontrolled introduction of various functionalities owing to its inherent stereochemical nature, the present finding involving a tandem single-step retro-aldol and intramolecular Friedel−Crafts alkylation sequence may be widely applicable to enantio- and diastereocontrolled preparation of a variety of natural products in a flexible manner. We are currently utilizing this hexahydronaphthalene synthesis for the construction of morphine[15] and related alkaloids.

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(14) Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 3301.
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